SYNTHESES AND REACTIONS OF THIENO (2, 3 - d) PYRIMIDINES

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SYNTHESES AND REACTIONS OF

THIENO [2,3-d] PYRIMIDINES

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October 1976

... dedicated to the ones I love

I express my sincerest thanks to Dr. Jim Clark, whose friendship and advice have been a source of encouragement.

I also express my gratitude to Allan and Hanburys (Research) Limited, Ware, Hertfordshire, for providing a studentship.

تحیات طیبہ سے

محمد شاہد شاکر

M Shahid Shakir

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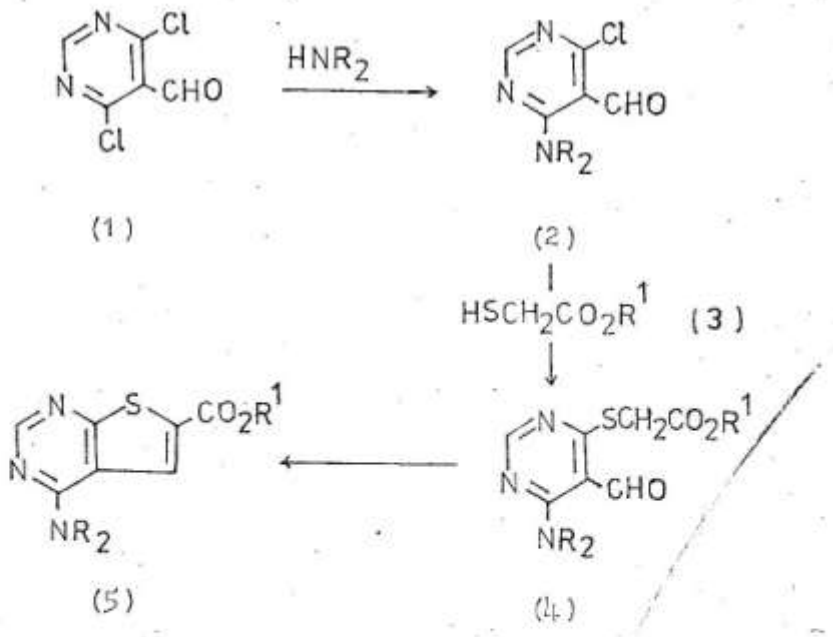
ABSTRACT

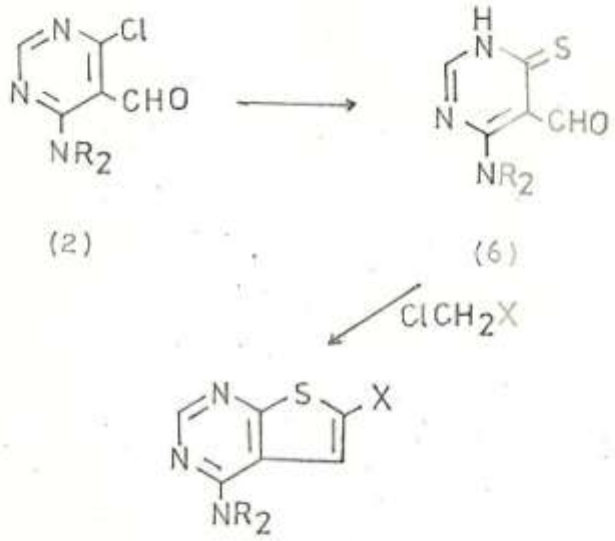
Thieno[2,3-d]pyrimidines have, so far, been synthesised mainly from thiophen derivatives. The work described in this thesis is largely concerned with a search for general methods of synthesising substituted thieno[2,3-d]pyrimidines from pyrimidines.

Condensation of 4,6-dichloropyrimidine-5-carbaldehyde (1) with amines yielded 4-substituted -amino-6-chloro pyrimidine-5-carbaldehyde (2) which reacted with thioglycolate (3; R^1 = Me or Et) to yield thienopyrimidines (5)(Scheme 1). In some cases the intermediates (4) were isolated and cyclised by further heating.



Scheme 1

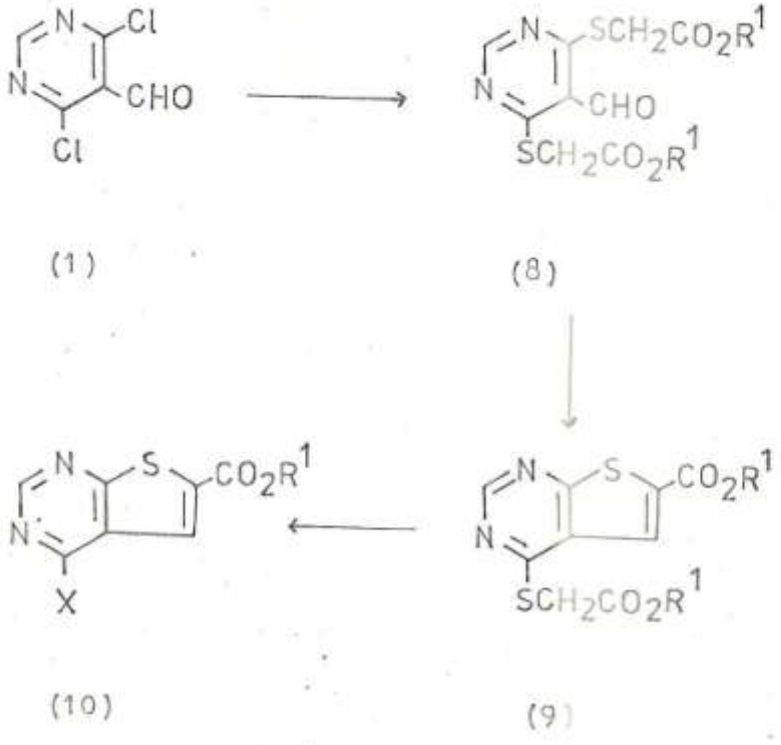
This method was useful for producing thieno[2,3-d]-pyrimidines with an ester group on position 6, but few active methylene compounds with the general formula XCH_2SH are readily available to vary the 6-substituent. However, compounds XCH_2Cl where X = ArCO, CN, CO_2Et were condensed with 6-substituted-amino-5-formyl-pyrimidine-4(3H)-thiones (6) to yield thieno[2,3-d]-pyrimidines (7) (Scheme 2) with various groups at position 6.



(2) (6) (7)

Scheme 2

Both the above methods start with condensation of a dichloropyrimidine containing two identical chlorine atoms with one mole of an amine. This was avoided by condensing the pyrimidine (1) with an excess of a thioglycolate (3; R^1 = Me or Et) to give a very high yield of a 4-alkoxycarbonylmethylthiothieno[2,3-d]-pyrimidine (9) (Scheme 3). The intermediate (8) could be isolated if required.

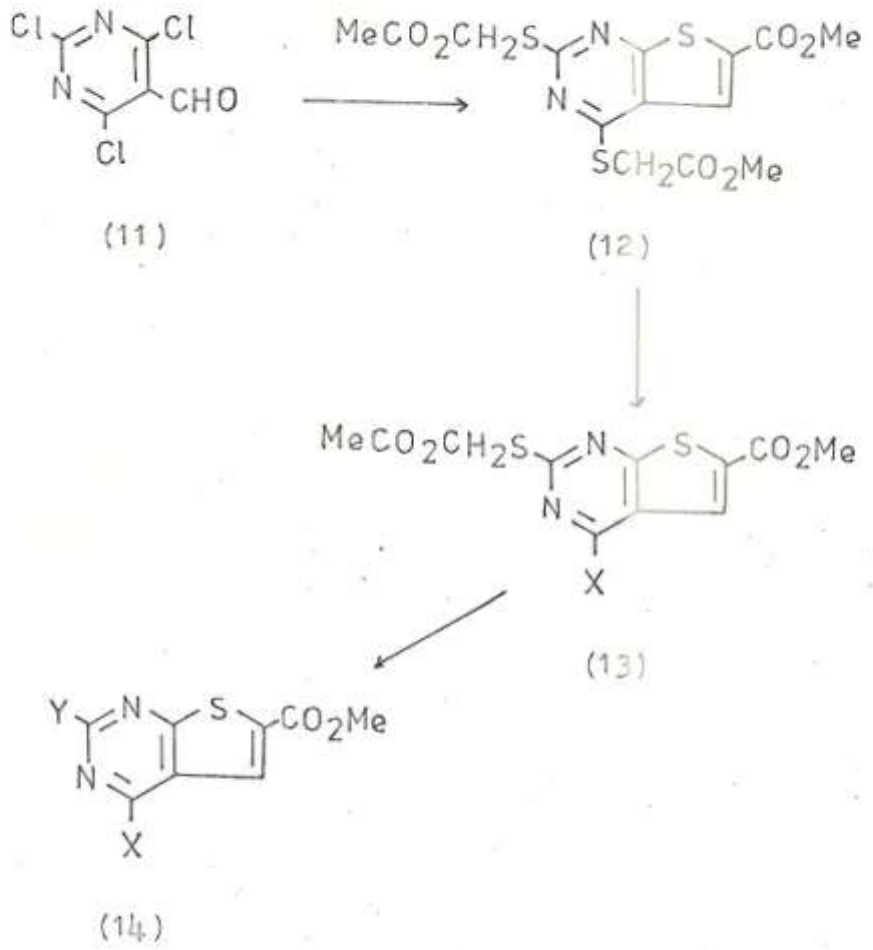


(1) (8) (9) (10)

Scheme 3

The alkoxycarbonylmethylthio group served as a good leaving group in nucleophilic substitution, so the thienopyrimidines (9) could be converted to a wide range of compounds (10; X = NR_2, OR or SR) by reaction with, for example, amines or hydroxide, alkoxide or thio-alkoxide ions. The range of products was extended still further by using 2,4,6-trichloropyrimidine-5-carbaldehyde (11) as starting material to produce the bis methoxy-carbonylmethylthiothienopyrimidine (12) which could be

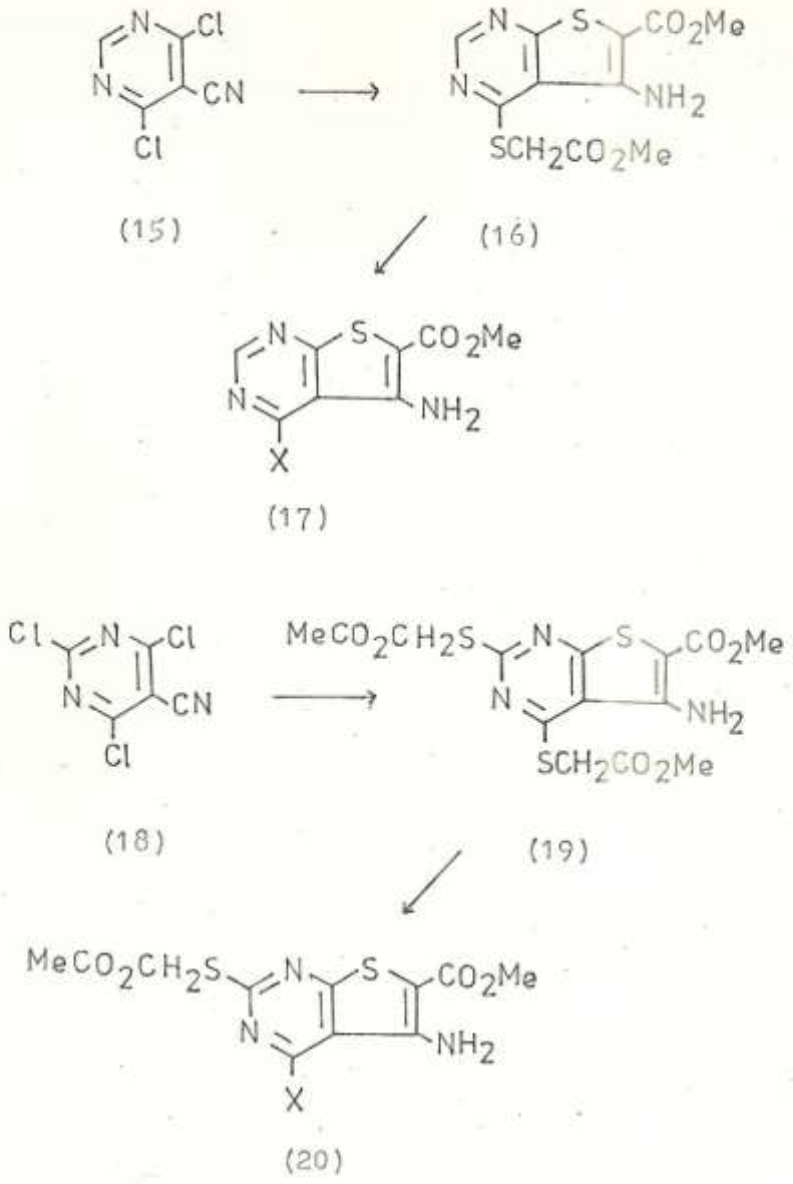
reacted with identical or different nucleophiles in stages to yield the thienopyrimidines (13; X = NR_2, OR or SR) and (14; Y = NR_2, OR or SR) (Scheme 4).



(11) (12) (13) (14)

Scheme 4

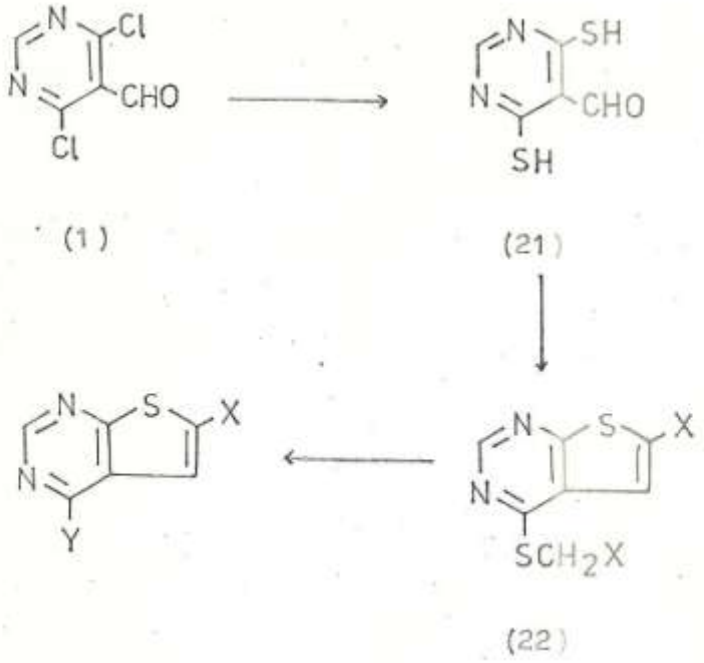
By using 4,6-dichloro- (15) or 2,4,6-trichloro- (18) pyrimidine-5-carbonitrile as starting material, 5-aminothienopyrimidines (16) and (19) were made and converted by nucleophilic replacement of their 4-methoxycarbonylmethylthio groups into various substituted thienopyrimidines (17) and (20) (Scheme 5).



Scheme 5

In order to introduce groups other than alkoxycarbonyl into position 6 the readily prepared 4,6-dimercaptopyrimidine-5-carbaldehyde (21) was condensed with halogeno compounds such as chloroacetonitrile, chloroacetamide, phenacyl halides or alkyl chloroacetates.

When an excess of the halogeno compound was used, a substituted methylthio group was introduced at position 4 and the thieno-pyrimidine (22) had the appropriate substituent at position 6 (Scheme 6). 4,6-Dimercapto-pyrimidine-5-carbonitrile was used in a similar way to give analogous 5-amino compounds.



Scheme 6

The ease with which various substituents in the thieno-pyrimidine systems can be displaced by nucleophiles has been investigated. Conversion of some of the thienopyrimidines to tricyclic compounds has been carried out.

HISTORICAL

The work in this thesis is concerned with certain pyrimidine and thieno [2,3-d] pyrimidine derivatives. The literature on pyrimidines and thiophens is very extensive and has been adequately reviewed elsewhere.[1-4] The following historical survey therefore deals only with the syntheses and properties of thienopyrimidines and derivatives containing the thienopyrimidine nucleus.

CHAPTER I

THIENOPYRIMIDINES

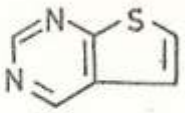
Introduction

The field of thienopyrimidines has only recently been developed. Since the preparation of the first derivative in 1947,[5] very little interest in the subject was shown until the late 1960s. The intensive current effort directed towards the preparation of biologically active compounds has led to considerable attention being given to this branch of chemistry. Interest in the compounds arises from their structural similarities to physiologically active compounds. For example, the thieno [2,3-d] pyrimidine ring system which is isosteric with that of the known active diaminoquinazolines has now been examined with regard to dihydrofolate reductase activity.[6]

Nomenclature

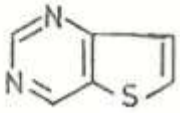
Nomenclature was varied when thienopyrimidines first appeared in the literature, but when more research papers began to appear, the system in "Chemical Abstracts" was universally adopted. The three thienopyrimidine systems (1-3) are:

A. Thieno [2,3-d] pyrimidine



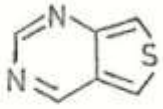
(1)

B. Thieno [3,2-d] pyrimidine



(2)

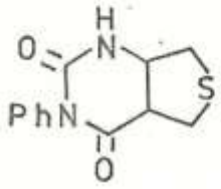
C. Thieno [3,4-d] pyrimidine



(3)

The first derivative of any of these ring systems was reported in the literature in 1947, and it was the thieno [3,4-d] pyrimidine (4) described as thieno [3,4-d] - uracil.[5] The thieno [3,2-d] pyrimidine (5) was first

described in 1948 as thianaphtheno [2',3',5,6] pyrimidine,[7] while the first thieno [2,3-d] pyrimidine (6), reported in 1953, was described in accordance with the "Chemical Abstracts" system.[8]



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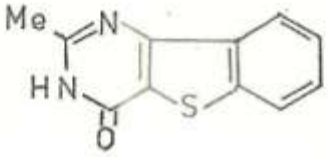

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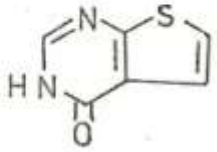


(6)

CHAPTER II

THIENO [2,3-d] PYRIMIDINES

Introduction

The earliest syntheses of thieno [2,3-d] pyrimidines were described by Baker et al[8] in studies of analogues of the hydrangea alkaloids. They reported in 1953 that the action of methanolic ammonia on methyl 2-amino-methyleneaminothiophen-3-carboxylate (7) gave a low yield (4%) of thieno [2,3-d] pyrimidin-4-one (6). Subsequently, other papers appeared in which syntheses of thieno [2,3-d] pyrimidines were reported. These syntheses go mainly via thiophens, pyrimidines or thieno [2,3-d] oxazines. Two Ph.D. theses have been devoted to the syntheses of thieno [2,3-d] pyrimidines from thiophens.[9,10]

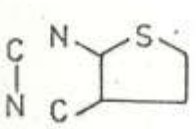
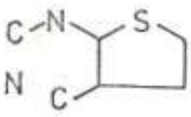
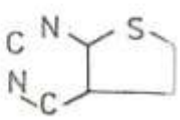
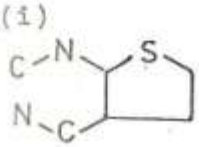
(7) (6)

Syntheses from Thiophens

Syntheses of thieno [2,3-d] pyrimidines from thiophens may be classified according to the atoms of the pyrimidine ring which are finally introduced into the thiophen derivatives. Four classes are described (Table 1).

Table 1

Classification of Thieno [2,3-d] pyrimidine Syntheses

Class A	Class B	Class C	Class D
			(i) 

In the lists below, references are in parentheses.

Reagents

formamide or formamidine (11-30)

imidates (27, 31, 33)

urea or isocyanates (11, 26, 34-41)

thiourea or isothiocyanates (42-54)

isourea or isothiourea (55, 56)

lactams (57, 58)

ethylcarbamate (26, 59-64)

chloroformamidines (65-69)

thioamides (70, 71)

Reagents

amines, hydrazine hydrate, ammonia or ammonium salts (72-80)

Reagents

aldehydes or ethyl chloroformate (81-84)

triethylorthoformate (26)

phosgene (37)

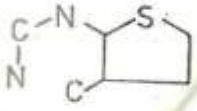
potassium xanthate (85-89)

cycloketones (90)

Cyclisation Solvents

glycerol (91-94)

acids or bases (95-98)

(ii) 

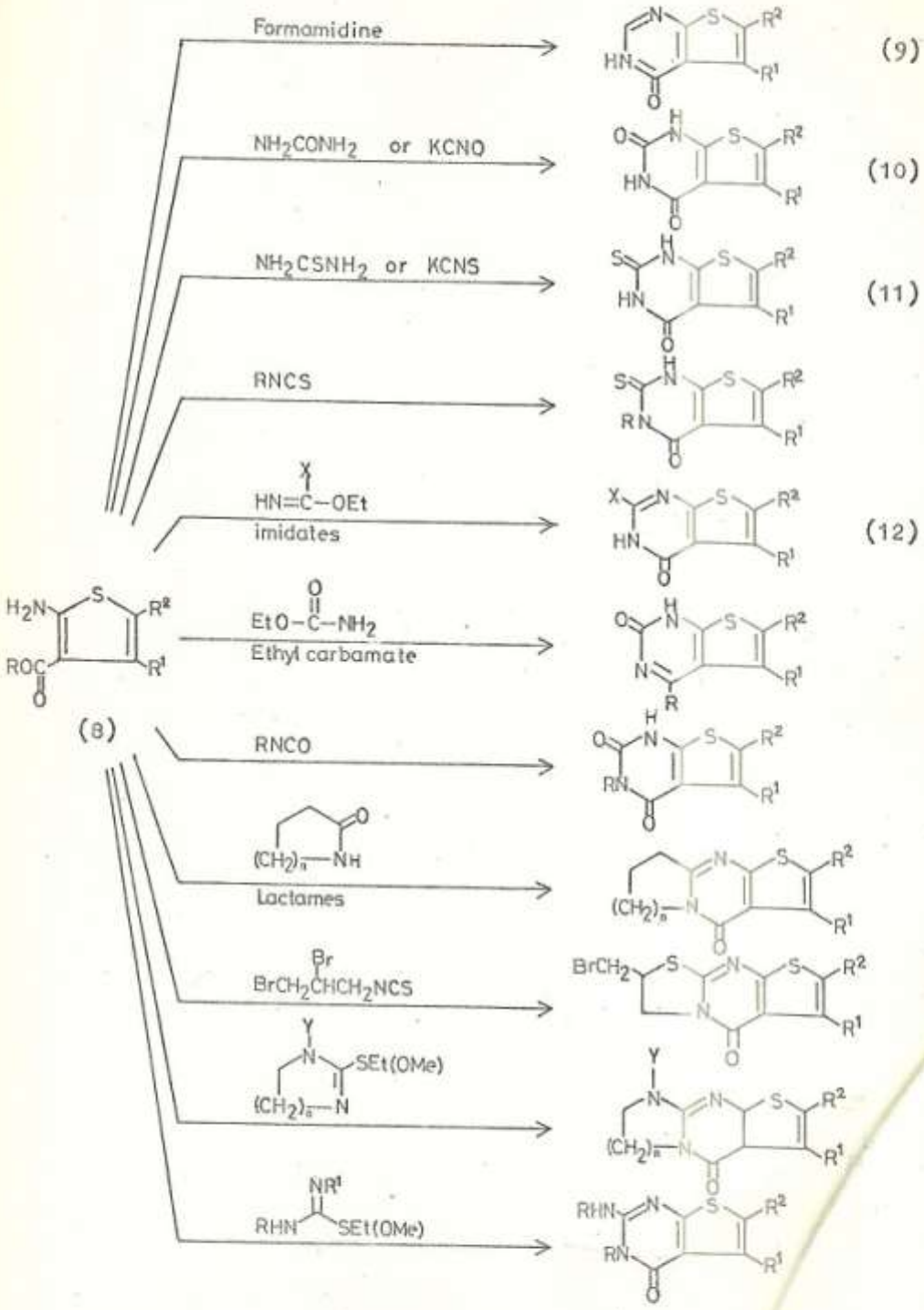
Cyclisation Solvents

dimethylformamide or sodium methoxide (99, 100)

bases (101-103)

acids (104, 105)

(iii) Rearrangement (106)


Formamidine
(9)
NH2CONH2 or KCNO
(10)
NH2CSNH2 or KCNS
(11)
RNCS
HN=C(X)–OEt
imidates
(12)
EtO–C(=O)–NH2
Ethyl carbamate
(8)
RNCO
(CH2)n–NH
Lactames
BrCH2CH(Br)CH2NCS
SEt(OMe)
(CH2)n–N
NR1
RHN
SEt(OMe)

Scheme 1

Class A

Substituted alkyl 2-aminothiophen-3-carboxylates (8 ; R = alkyl) yield a very wide range of thieno [2,3-d] -pyrimidin-4-ones (Scheme 1) when condensed with suitable reagents. For example, condensations with formamide, formamidine or formamidates yield 2-unsubstituted-4-ones (9). R^1 and R^2 may be hydrogen, alkyl, aryl or oxygenated substituents such as ethoxycarbonyl and acetoxyethyl, R^1 and R^2 together may also form a polymethylene or substituted polymethylene ring system.[11-31] The thieno-thiopyran (8 ; R = Et, R^1R^2 = $CH_2CHPhSO_2CHPh$) also behaves similarly on reaction with formamide.[22] The reactions of the aminothiophens (8 ; R = alkyl) with urea or potassium isocyanate give 2,4-diones (10); thiourea or isothiocyanates give 4-hydroxy-2-thiones (11); imidates give 2-substituted 4-ones (12) and isocyanates, isoureas or isothioureas give appropriate 2,3-di-substituted thieno [2,3-d] pyrimidin-4-ones (13) as detailed in Table 2 and Scheme 1.

Table 2

(8) (13)

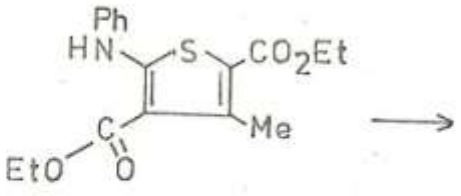
Table 2 (contd)

Reactants	Products	Reagents	References
R^1,R^2 = H,Me,Et, Ph or $(CH_2)_4$ R = Me	R^3 = H X = H,Me,CH_2Ph, Ph,CCl_3, (P)MeC_6H_4, NC $(CH_2)_4$, 2-Naphthyl or furyl.	imidates	26, 27, 31, 33
R^1,R^2 = H,Me, Ph or $(CH_2)_4$ R = Et	R^1,R^2 as in reactants R^3 = H,Me,CH_2-Ph or Ph X = OH	urea or isocyanate	11, 26, 34-41
R^1,R^2 = H,Me, Ph or $(CH_2)_4$ R = Me or Et	R^1,R^2 as in reactants R^3 = H,Me,Ph or $CH_2CH{:}CH_2$ X = SH,SK,SEt or SCOMe XR^3 = SCH(CH_2Br)-CH_2-	Thiourea or isothiocyanate	42-54
R^1 = H or Me, R^2 = H, Et, Bu CH_2CO_2H, CO_2Et, $(CH_2)_4$Me, or 2-imidazolin-2-yl; R^1,R^2 = $(CH_2)_3$, $(CH_2)_4$, CH_2 CH_2NMeCH_2	R^1,R^2 as in reactants R^3 = Me or Et X = NHMe or NHEt XR^3 = $N(Y)(CH_2)_n$ Where Y = H,Me,COMe $COCO_2Et$ or cyclo-hexyl. n = 2 - 4	isourea or isothiourea	55 - 56

Table 2 (contd)

Reactants	Products	Reagents	References
$EtO_2CCHCH_2CH_2$ or $EtO_2CCMeCH_2CH_2$ R = Me or Et			
R^1,R^2 = H, Me, PhCO, or $(CH_2)_4$ R = Me or Et	R^1,R^2 as in reactants XR^3 = $(CH_2)_{3-5}$	Lactam	57, 58

N-Substituted thienopyrimidines (15 and 17) can be made from substitutedamino thiophens (14 and 16) on reactions with methyl isocyanate,[41], urea[35] or ethyl carbamate.[26,59-64] R, R^1 and R^2 in starting material and products (16 and 17) may be hydrogen, alkyl or aryl and R^1, R^2 together may be a polymethylene ring system. Similarly, 2-aminothiophen-3-carbonitriles (18) with



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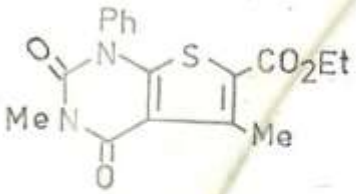
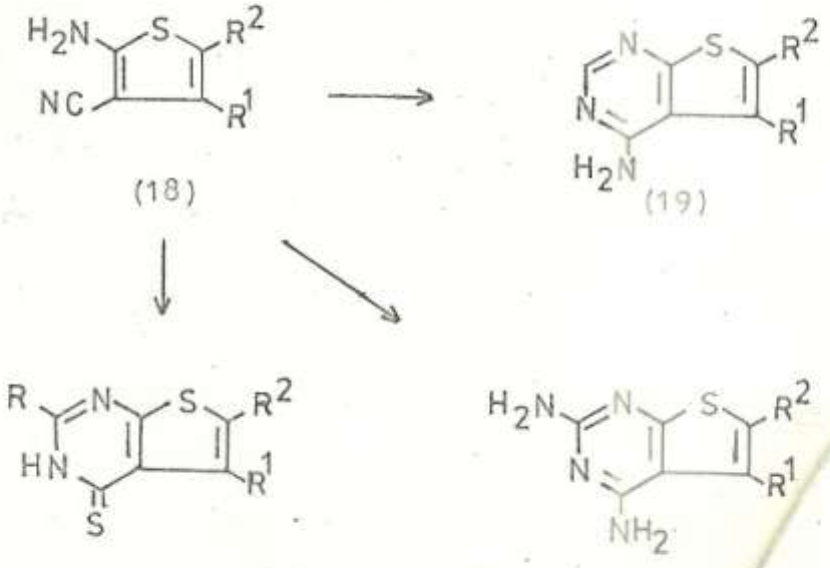


(15)

(16) (17)

formamide[29,30] give 4-aminothienopyrimidines (19); with chloroformamidine[65-69] give 2,4-diamino derivatives (20) and with thioamides[70,71] give the 4-thiones (21). R, R^1 and R^2 in these compounds (18-21) are similar to those described for (16 and 17).

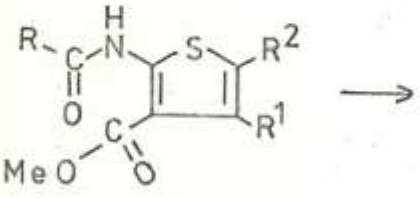


(18) (19)

(21) (20)

Class B

2-Acylaminothiophens (22) give 2,3-disubstituted thienopyrimidine-4-ones (23), when condensed with reagents such as alkylamine, anilines, hydrazine hydrate or ammonia[8,72-76] which provided the remaining nitrogen fragment. Similarly, with ammonium acetate, the thiophens (24)[8,77,78] and (26)[79] gave the derivatives (25) and (27) respectively, and with hydrazine hydrate the thiophen (28) gave the 4-imino derivative (29)[80]. In the compounds (22-27) R, R^1, R^2 and R^3 may be hydrogen, alkyl or aryl and R^1, R^2 together may be polymethylene or heterocyclic.



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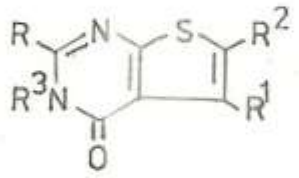

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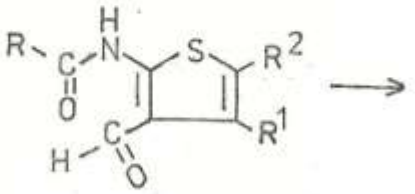

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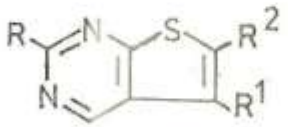

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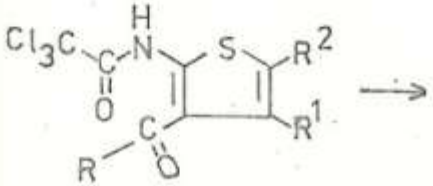

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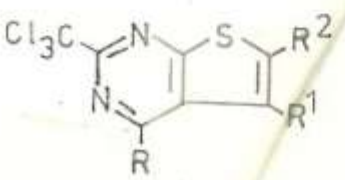


(27)

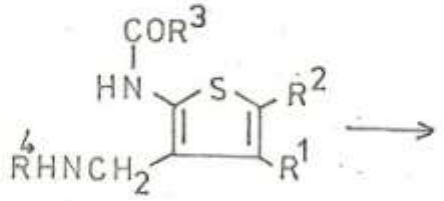
(28) (29)

Class C

2-Aminothiophen-3-carboxamides (30) gave thieno-pyrimidine-4-ones when reacted with reagents which provided the remaining carbon fragment. For example, condensations with triethyl orthoformate[26] gave the 4-ones (9 ; R^1 = Ph, R^2 = H or Me), phosgene[37] gave the 2,4-dione [10 ; R^1R^2 = $(CH_2)_4$] and with aromatic aldehydes[37] or ethyl chloroformate[81-83] gave the 2-substituted derivatives [12 ; R^1,R^2 = H, alkyl, aryl or $(CH_2)_4$; X = OEt or aryl].

(30) (12)

The thiophens (31) cyclised in formaldehyde[84] to give the reduced thienopyrimidines [32 ; R^1,R^2 = Me or $(CH_2)_4$, R^3,R^4 = alkyl or aryl]. The 2,4-dithiones (33) were made from the aminothiophen-3-carbonitriles (18 ; R^1 = Me, R^2 = CO_2Et ; R^1,R^2 = $(CH_2)_4$ or $CH_2CH_2N(Me)CH_2$] with potassium xanthate.[85-89]



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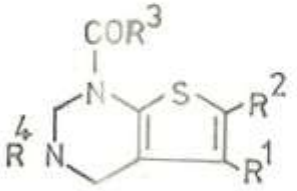

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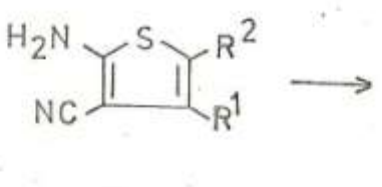

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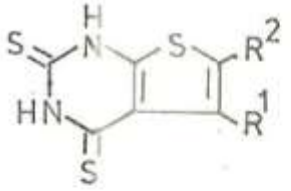
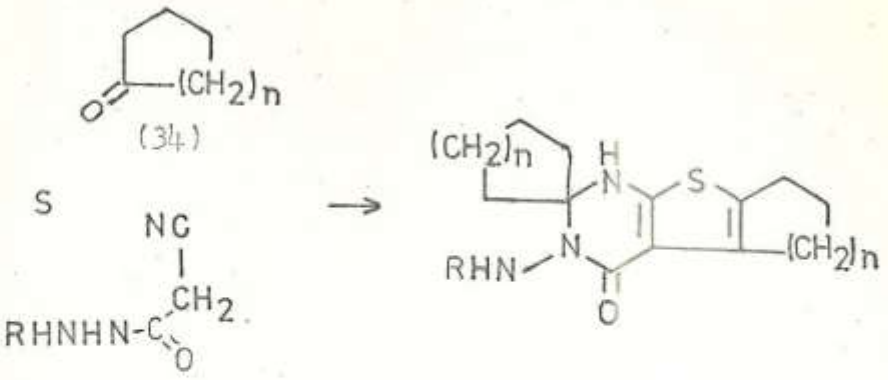


(33)

The cycloketones (34 ; n = 1 or 2), when treated with a cyanomethylcarbohydrazine or hydrazide (35 ; R = H or COMe) and sulphur in the presence of basic catalyst, gave the 1,2-dihydrothienopyrimidin-4-ones (36).[90]

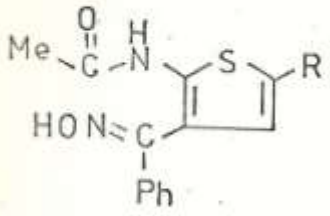


(34) (35) (36)

Class D

(i) 2-Acylaminothiophen-3-carboxamides (37), when heated in a suitable solvent such as glycerol,[91-96] ethyl chloroformate,[37,83] or a base[95,96] undergo thermal cyclisation to give the 2-substituted thieno-pyrimidin-4-ones [12 ; R^1,R^2 = H or $(CH_2)_4$; X = H, Me, OEt, aryl or heteroaryl]. Similarly, the thiophen-ketoximes (38 ; R = H or Cl) cyclise under acidic conditions[97,98] to give the appropriate 3-oxides (39).

(37) (12)



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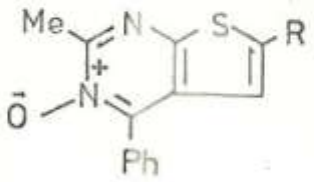


(39)

(ii) Cyclisation of the thiophens (40) in dimethylformamide and sodium methoxide[99,100] gave the 4-aminothienopyrimidines [19 ; R^1R^2 = Me, $(CH_2)_4$ or heteroaryl]. The reduced thiophens (41) gave bicyclic products [42 ; R, R^1, R^2, R^3, R^4 = H, Me or Ph or R^1R^3 = $(CH_2)_4$; X = alicyclic amino] when refluxed with amines.[101,102] The thienopyrimidin-4-ones (44, 46 and 48) were prepared by cyclisation of the thiophen esters (43, 45 and 47 respectively) under acidic or basic conditions.[103-105]

(40) (19)

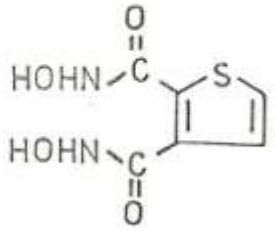
(41) (42)

(43) (44)

(45) (46)

(47) (48)

(iii) Sodium 2,3-thiophendicarbohydroxamate (49) with benzene sulphonyl chloride gave a 3:1 mixture of thieno [2,3-d] - and [3,2-d] pyrimidines (50 and 51 respectively)[106] presumably via two different Beckmann rearrangement reactions.



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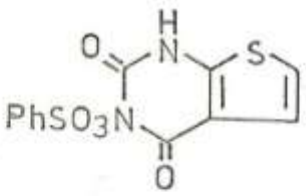

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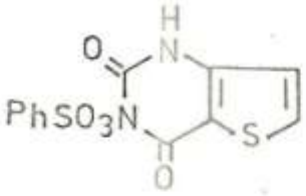
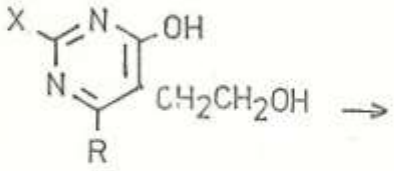


(51)

Syntheses from Pyrimidines

Ring closure of suitably substituted mercapto-pyrimidines gives a wide range of thienopyrimidines. For example, dehydrations of 5-β-mercaptoethylpyrimidines (52 ; R = H or Me, X = NH_2 or SH)[107] or 4-acylmethyl-thiopyrimidines (54 ; R = OEt, Me or Ph)[108,109] by polyphosphoric acid give the appropriate derivatives (53) and (55). Cyclisation of similar pyrimidines (56 ; R^1 = Me or $C_6H_4Br_{(p)}$, R^2 = H or CH_2Ph) in diphenyl ether gave thienopyrimidines (57).[6,110,111]



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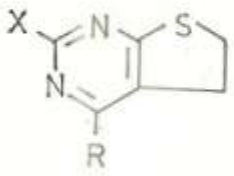

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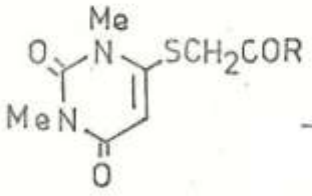

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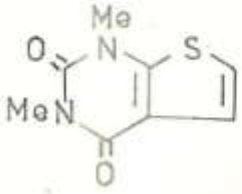


(55)

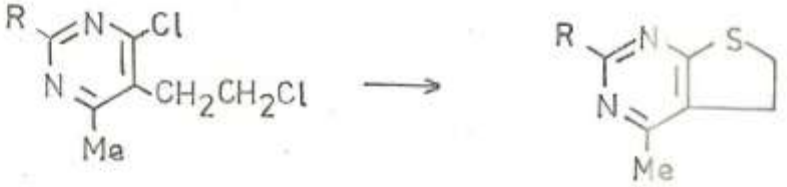
(56) (57)

Cyclisations of the 5-substituted pyrimidines (58) and (60 ; R = alkoxy, Ph or arylamino, R^1 = Me, Ph, SMe or NMe_2, R^2 = H or Me) under basic conditions gave the thienopyrimidines (59)[112] and (61)[113] respectively. The thienopyrimidines (63 ;R=H, Me or SMe, R^1 = Me, SH or NMe_2) were made by treatment of the pyrimidines (62 ; X = SH or Cl) with 98% sulphuric acid or thiourea.[114] Similarly, the chloropyrimidines (64 ; R = H or Cl) when treated with thiourea[115] in ethanol gave the reduced derivatives (65 ; R = H or SH). Photolysis of the pyrimidine (66) in acetonitrile yielded the benzothienopyrimidine (67).[116]

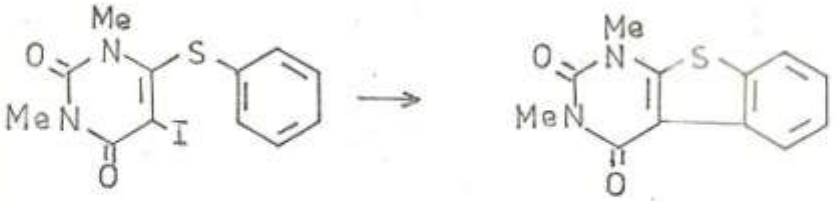
(58) (59)

(60) (61)

(62) (63)



(64) (65)



(66) (67)

Syntheses from Oxazines

Thieno [2,3-d] oxazines (68) and compounds which contain the thieno [2,3-d] oxazine system are converted to thieno [2,3-d] pyrimidines (69 ; R = H, alkyl, aryl or alkylamino ; R^1 = Me, R^2 = COPh, R^1R^2 = $(CH_2)_4$ or 2-substituted pyrimidyl ; X = H or alkyl) when treated with alkylamines, anilines or hydrazines.[117-121]

(68) (69)

CHAPTER III

THIENO[3,2-d] PYRIMIDINES

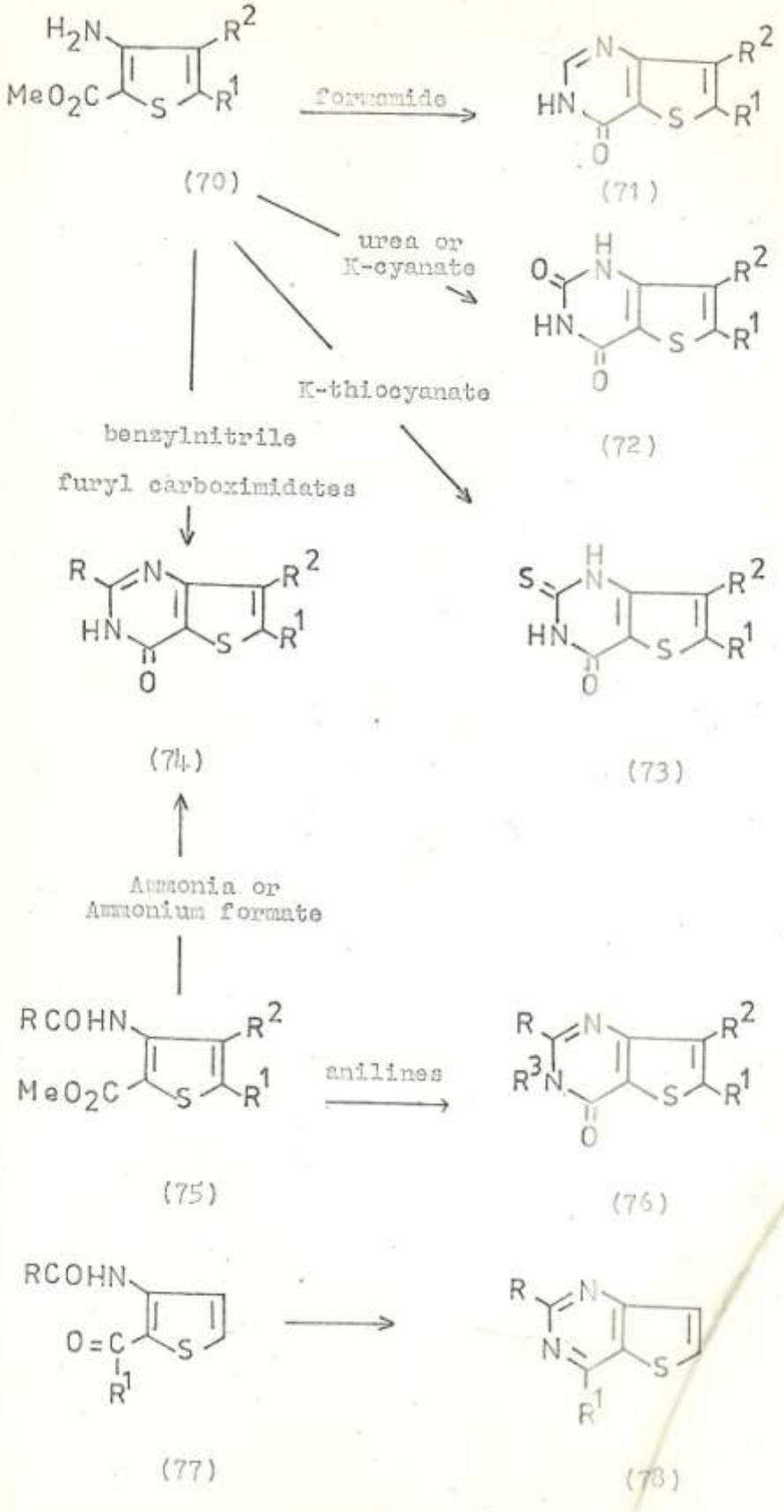
Introduction

The first thieno[3,2-d] pyrimidines reported in the literature were described as thianaphtheno[2',3',5,6] - pyrimidines by McCleland and Stammers.[7] Thieno[3,2-d] - pyrimidines have been mainly made from thiophen or oxazine intermediates.

Syntheses from Thiophens

Methyl 3-aminothiophen-2-carboxylates (70) yield a very wide range of thieno[3,2-d] pyrimidine-4-ones (Scheme 2) when condensed with suitable reagents. For example, condensations with formamide give 2-unsubstituted 4-ones (71 ; R^1,R^2 = H, aryl or heterocyclic)[122-125]; urea or potassium cyanate give 2,4-diones (72);[123,126,127] potassium thiocyanate give 4-hydroxy-2-thiones (73)[123] and benzyl nitrile[123] or furyl carboximidates[31,32,128-131] give 2-benzyl or 2-furyl derivatives (74 ; R^1,R^2 = H or Me) respectively.

Methyl 3-arylaminothiophen-3-carboxylates (75) with alcoholic ammonia or ammonium formate in formamide give 2-substituted 4-ones (74)[7,13,132-137] and with anilines give 3-aryl derivatives (76).[72,74,118] Similarly, 2-acyl-3-acylaminothiophens (77) with ammonium formate[136,137] give the appropriate derivatives (78). R,R^1 and R^2 in

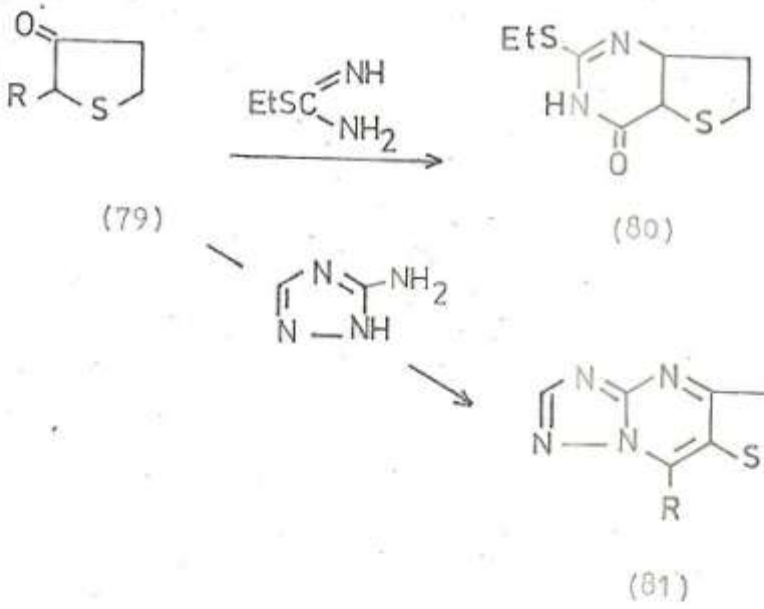


(70) (71) (72) (73) (74) (75) (76) (77) (78)

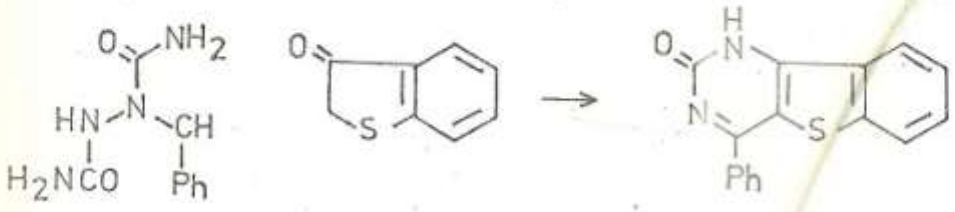
Scheme 2

these compounds (75-78) may be hydrogen or methyl and R^3 in (76) may be aryl.

The thiophen-β-keto ester (79 ; R = CO_2Me) with S-ethyl-thiourea[140] or 5-amino-1,2,4-triazole[142] gives 1,2-disubstituted derivatives (80) or (81 ; R = OH) respectively, while the β-ketonitrile (79 ; R = CN) with the same triazole gives the amino analogue (81 ; R = NH_2).[142] Similarly, the 3-thianaphthenone (83) with benzalbisurea (82) in acetic acid gives the tricyclic compound (84).[143]



(79) (80) (81)



(82) (83) (84)

Sodium 2,3-thiophendicarbohydroxamate (49) in benzene sulphonyl chloride rearranged to give a 3:1 mixture of thieno [2,3-d] - and [3,2-d] pyrimidine-2,4-diones (50 and 51)[106] as described earlier (p. 18)

Syntheses from Oxazines

Compounds (85) containing the thieno [3,2-d] oxazine system are converted to analogues (86) with the thieno-[3,2-d] pyrimidine system on treatment with alcoholic ammonia or amines.[7,118,121,125] Ring A may be a benzene, d-fused pyrimidine or d-fused pyrazine ring while the 3-substituent R in the product (86) may be hydrogen or an alkyl or substituted alkyl group.

(85) (86)

CHAPTER IV

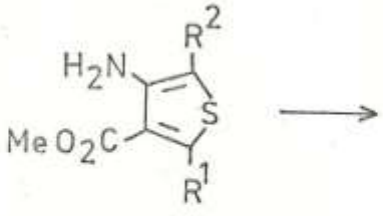
THIENO [3,4-d] PYRIMIDINES

Introduction

The earliest syntheses of thieno [3,4-d] pyrimidines were reported by Baker et al[5] in 1947. More syntheses later appeared in the literature and these also go via thiophen intermediates except for one example which goes via a pyrimidine precursor.

Syntheses from Thiophens

Substituted methyl 4-aminothiophen-3-carboxylates (87 ; R^1 = H or Me, R^2 = H or 2-thienyl) give thieno-[3,4-d] pyrimidine-4-ones (88) on condensation with formamide[174] or ammonium formate in formamide.[8] Condensations of the reduced thiophens (89 ; R = Me or Et) with S-ethylthiourea[175-177] or acetamidine salts[178,179] give 2-substituted 4-ones (90 ; X = SEt or Me).



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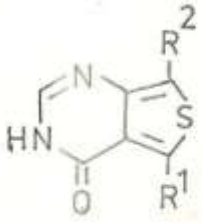

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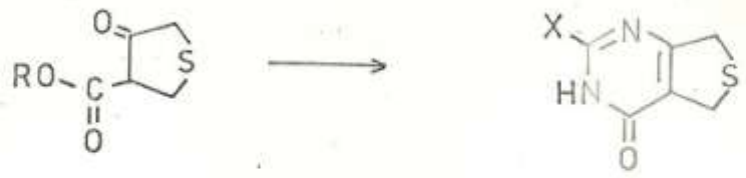
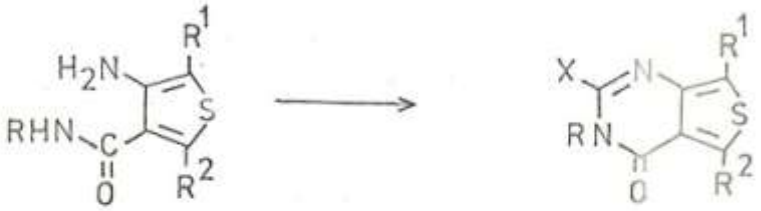


(89) (90)

Condensations of alkyl 4-acylaminothiophen-3-carboxylates (91 ; X,R = H or Me) with ammonia, alkylamines or anilines give respectively, 3-unsubstituted-, 3-alkyl or 3-aryl derivatives (92 ; X = H or Me, R^1 = H, alkyl or aryl).[180,181] Similar derivatives (94 ; R,X = H or Me, R^1,R^2 = Me,Ph,SMe or CO_2Me) are also made by condensation of 4-amino-3-(substituted)carbamoylthiophens (93) with acetic anhydride[182,183] or triethyl orthoformate.[122] Cyclisation of methyl 4-uriedothiophane-3-carboxylates (95 ; R = H, alkyl or aryl, R^1,R^2 = H, alkyl or carbalkoxy) under acidic conditions give reduced compounds (96).[5,184-190] Similarly, the thiophanes [97 ; R = H or $(CH_2)_4CO_2Me$] gave the derivatives (98 ; R^1 = COMe) in acetic anhydride[188-189] and methyl 4-ureido-thiophen-3-carboxylate (91 ; R = Me, X = NH_2) cyclised to the 2,4-dione (92 ; R^1 = H, X = OH) in dilute hydrochloric acid.[191]

(91) (92)

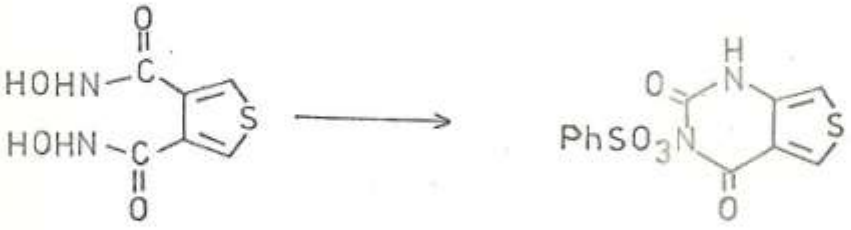


(93) (94)

(95) (96)

(97) (98)

Rearrangement of sodium 3,4-thiophenedicarbohydroxamate (99) in benzene sulphonyl chloride gives 67% of 3-phenylsulphonyloxythieno [3,4-d] pyrimidine-2,4(1H,3H)-dione (100).[106]



(99) (100)

Synthesis from a Pyrimidine

Reaction of 5-hydroxymethyluracil-4-carbaldehyde (101) with boron trifluoride-diethyl ether complex in thioacetic acid gives the 2,4-dione (102).[192]

(101) (102)

CHAPTER V

BIOLOGICAL STUDIES

Introduction

Early workers in the field seemed to be concerned with simply synthesising derivatives of the three thienopyrimidine systems, but the emphasis has now shifted to the biological properties of the compounds.

Thieno [2,3-d] pyrimidines

Some 2,4-diamino- (103) and 2,4-bis-substituted-amino compounds are dihydrofolate reductase inhibitors. High activity is favoured by bulky 6-substituents (R^1) and small 5-substituents (R). The low pKa values of the compounds reduce their utility since a protonated species is required for enzyme binding and acidic solutions are required for maximum activity.[6]

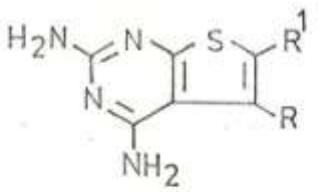
A large number of diamino derivatives showed antimalarial activity at high doses, but all were inferior to previously synthesised pyrimethamine analogues. For example, the compounds (103 a-c) were active at 640 mg/kg against *Plasmodium berghei* in mice and the derivative (103 d) was active against *P. gallinaceum* at 120 mg/kg in chicks. The derivatives (103 e-g) showed antimetabolite activity against *Streptococcus faecium*.

The thienopyrimidines (103 c and h) were used as anthelmintic and antiprotozoal agents and as antibacterial agents against E. Coli and L. Casei, but other derivatives (103 i-j) gave negative results when tested for radiation protection and antimalarial properties.

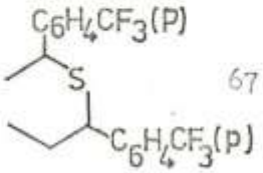
Some 2,3-disubstituted thienopyrimidinones (104) were used as hypocholesterolemic drugs, sedatives and antitussives. For example, the derivative (104 a) given at 100 mg/kg iv., lowered the cholesterol blood level of rats by 30%.[42] The derivative (104 b) has weaker hypnotic effect, in mice, than methaqualone,[73] while still other derivative (105 ; R = H or Me) had some sedative activity.[74]

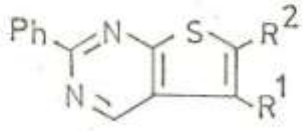
1,4-Disubstituted derivatives (106) were useful as uricosurics, antiphlogistics, analgesics and diuretics.[79] For example, mice treated with 20 mg/kg urea iv. and 100 mg/kg of the derivative (106 a) orally, excreted urea at a rate of 39.2 ± 8.2 µg/100 g in 5 hours compared with 8.3 ± 1.4 µg/100 g for control.[59]

Some 2,4-disubstituted thienopyrimidines (107) have bactericidal and trichomonacidal properties;[33] 2-substituted derivatives (108) were central nervous system depressants,[112] and the partially reduced compounds (109) acted as muscle relaxants, sedatives and antiinflammatories.[101,102] NR_2 in these compounds (107-109) may be substituted amino group; R^1,R^2,R^3 or R^4 may be hydrogen or alkyl and R^1R^2 together may be a polymethylene.



(103)

	R	R^1	References
a	$(CH_2)_6$		66
b			67
c	Me	CH_2Ph	
d	$CHMeCH_2CHMeCH_2$		66
e	Me	Ph	68
f	Me	$C_6H_3Cl_2(3,5)$	68
G	$CH_2CH_2CHMeCH_2$		66
h	H	$C_6H_5Br(4)$	111
i	Me	Me	29
J	$(CH_2)_4$		29



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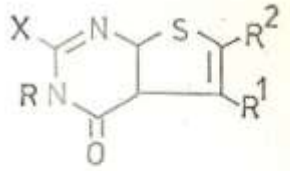
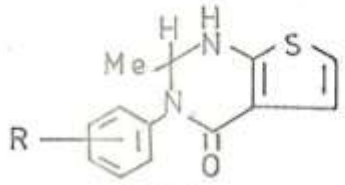


(104)

a X = SH, R,R^1 = H, R^2 = Me

b X = Me, R = Substituted Ph, $R^1 = R^2$ = H



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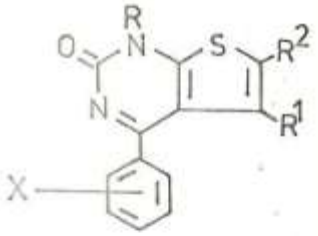
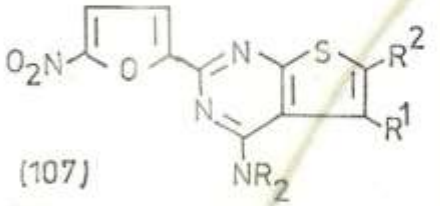


(106)

a, X = H, $R = R^1$ = Me, R^2 = Cl



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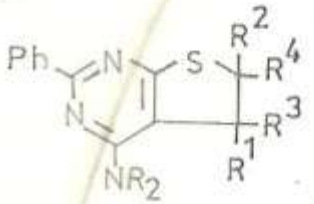
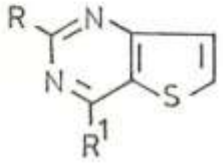


(109)

Thieno [3,2-d] pyrimidines

The thieno [3,2-d] pyrimidines (110-112) have cardiovascular, diuretic, analgesic, sedative, anti-rheumatic, antiphlogistic, cytostatic, bacteriostatic and fungistatic actions depending on the nature of R and R^1. The cardiovascular activity is especially marked when R or R^1 in (110-112) is an N-methylpiperazino group. Compounds (110-112) having R = alkoxy have especially good sedative action. These compounds may be administered orally, rectally or parenterally.[123]



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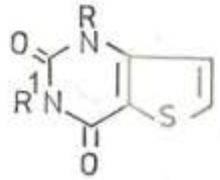
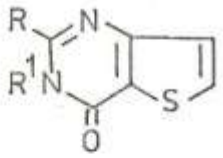


(111)

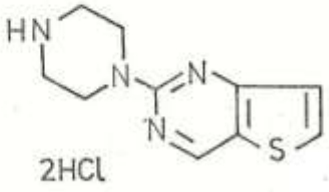


(112)

2,4-Disubstituted amino derivatives were useful for inhibition of thrombocyte-aggregation in blood.[128-171] For example, 2-piperazinothieno [3,2-d] pyrimidine dihydro chloride (113) inhibited the platelet aggregation induced by aggregating agents in vitro. High concentrations of the thienopyrimidine (i.e. 10^{-3}M) reversed the

platelet aggregation induced by ADP, inhibited the uptake of C^{14} labeled adenosine and partly of serotonin and inhibited the glycolytic pathway. Oxygen consumption was not inhibited.[165]

An improved general method was devised by Prox et al for identification of drug metabolite structures using the thienopyrimidine (114).[172,173]



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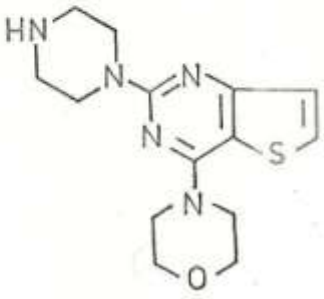
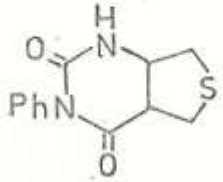


(114)

Thieno [3,4-d] pyrimidines

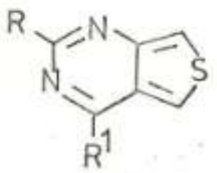
In order to prepare biologically active compounds such as biotin, Baker et al[5] synthesised the reduced thieno [3,4-d] pyrimidine (115). The hydrochloride



(115)

salts of the thienopyrimidines (116 ; R or R^1 = substituted amino) show cardiac stimulation in dogs and analeptic activity in rabbits at 2.5 mg/kg which is equal to that of a 6-fold dosage of diethylnicotinamide.[191]

Reduced 2,4-disubstituted derivative (117) possesses valuable pharmaceutical properties such as cardiovascular, sedative, diuretic, analgesic and cytostatic activity.[175-177] Similarly, 2,3-disubstituted derivatives (118 ; R = Me or Et, R^1 = o-tolyl, 2-Cl-3-pyridyl or 2-Cl-p-tolyl) show antispasmodic activity in rats equal to that of methaqualone hydrochloride.[181] Katz et al[179] described processes for altering the flavours and aromas of products including foods and tobacco by adding small but effective amounts of reduced thieno [3,4-d] pyrimidines (119) where R-R^5 are the same or different and represent hydrogen or alkyl groups.



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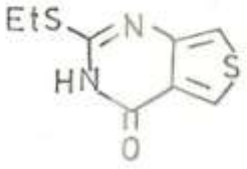

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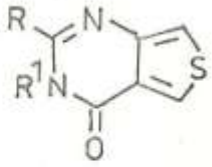

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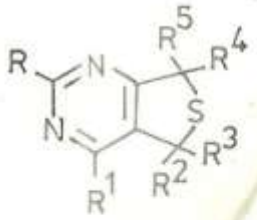


(119)

DISCUSSION

It is clear from the historical review in the previous chapters that relatively few thienopyrimidines have been made from pyrimidine intermediates. The rest of this thesis describes efforts to develop syntheses capable of giving a wide range of substituted thieno[2,3-d]pyrimidines from pyrimidines and in particular to make available thieno[2,3-d]pyrimidines capable of subsequent conversion to tricyclic compounds which are of interest as potential drugs.

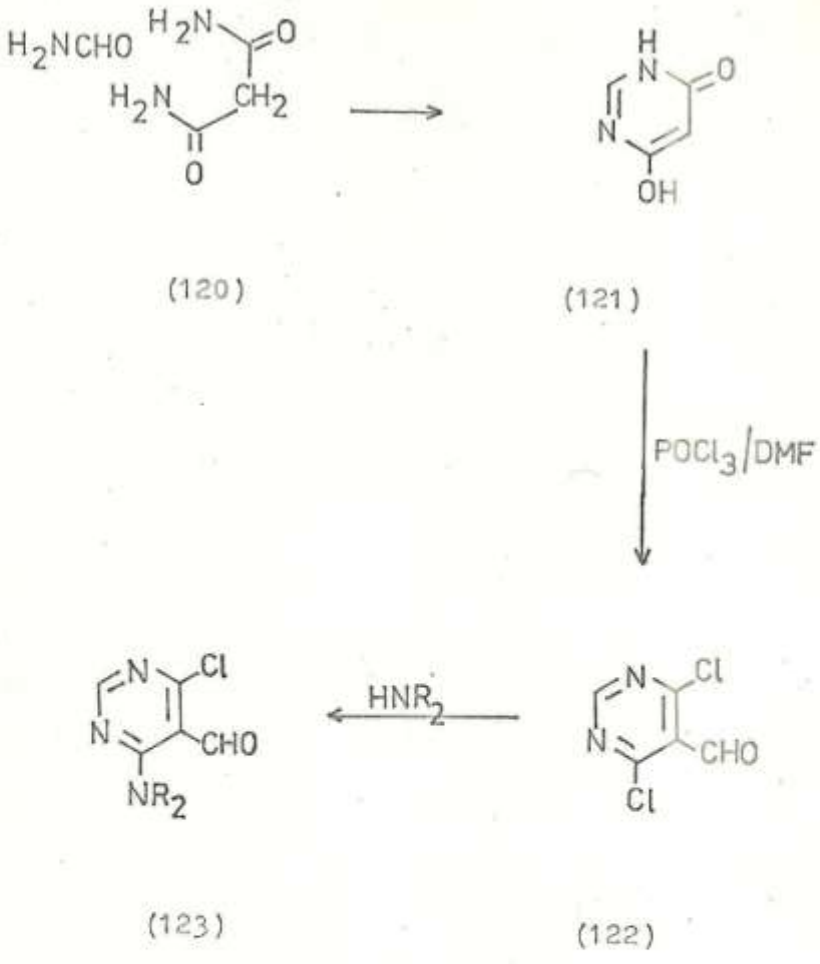
CHAPTER VI

SYNTHESES OF THIENO[2,3-d]PYRIMIDINES FROM 4-SUBSTITUTED AMINO)-6-CHLOROPYRIMIDINE-5-CARBALDEHYDES

A few thieno[2,3-d]pyrimidines had already been made from 4,6-dichloropyrimidine-5-carbaldehyde[113] and as a first step in the present researches this work was developed further. The route employed involved replacing one chlorine atom of the dichloropyrimidine with the desired substituent, usually a substituted amino group, and then building on the thiophen ring by reaction with an alkyl thioglycolate.

Part 1

4,6-Dichloropyrimidine-5-carbaldehyde[193] (122), the starting material employed in the preparation of the 4-substituted amino)-6-chloropyrimidine-5-carbaldehydes[194] (123 a-j) was synthesised by a series of reactions (120) to (123) in Scheme 3. Condensation of malonamide[195] (120) with formamide in ethanolic sodium ethoxide gave 4-hydroxy pyrimidin-6(1H)-one[196] (121). Vilsmeir formylation of the latter and simultaneous introduction of two chlorine atoms was carried out in phosphoryl chloride and dimethylformamide to give 4,6-dichloro-pyrimidine-5-carbaldehyde (122).



(120) (121) (122) (123)

	NR_2
a	$NHMe$
b	$NHEt$
c	$NHCH_2CH{:}CH_2$
d	$NHCH_2Ph$
e	$N(CH_2)_4$
f	$N(CH_2)_5$
g	$N(CH_2)_6$
h	$N(CH_2)_2O(CH_2)_2$
i	NMe_2
j	$NEtPh$
k	NH_2

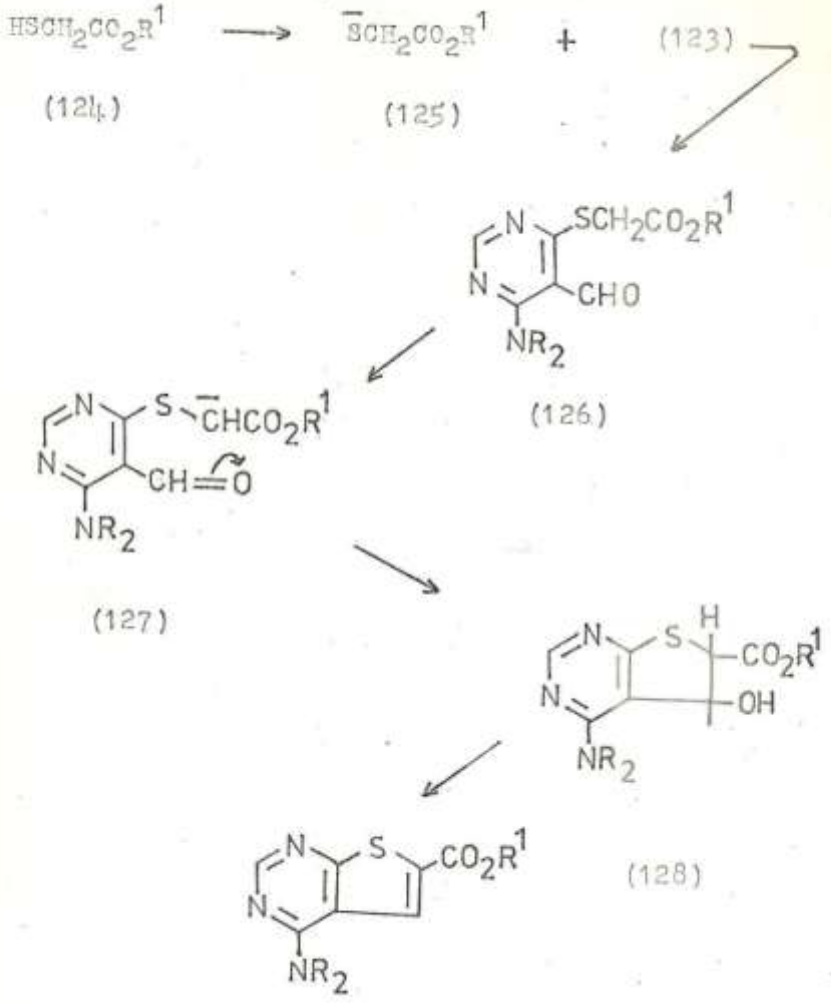
Scheme 3

Both chlorine atoms in the dichloropyrimidine (122) are in the most favoured position for activation by the formyl group and the ring nitrogen atoms, so reaction of this pyrimidine with amines in some solvents may result in the replacement of both chlorine atoms to give bis-substituted derivatives even at room temperature.[197] This difficulty was avoided by converting highly basic amines such as pyrrolidine, diethylamine or piperidine into their less reactive acetate salts before condensation. The method is illustrated by the formation of 4-chloro-6-pyrrolidino pyrimidine-5-carbaldehyde (123 e) on treatment of the dichloropyrimidine (122) with two molecular equivalents of pyrrolidine acetate (at pH 8) in dioxan at room temperature. Two equivalents of the amine are used so that the product is obtained as a free base together with a molecule of the amine hydrochloride. The less basic amine morpholine (pKa 8.7 at 25)[198] was exceptional and the free amine gave the pyrimidine (123 h). When condensations were carried out in chloroform using one molecular equivalent of an amine and one of triethylamine at 0° higher yields of aminopyrimidines (123 a-j) were obtained than had been obtained from reactions in dioxan and there was little trouble with bis-substitution. The 4-amino derivative (123 k) was prepared by passing ammonia gas through a solution of the dichloropyrimidine (122) in benzene at 0°.

The remaining chlorine atom in each pyrimidine (123 a-k) is still reactive towards nucleophilic replacement even at room temperature. Compounds of the general

structure $HSCH_2CO_2R^1$ (124 ; R^1 = Me or Et) are acidic and in the presence of strong bases give anions (125) which attack the chloropyrimidine (123) to yield intermediates (126 ; R^1 = Me or Et), which could be isolated when a restricted amount of base was used and conditions of reaction were kept very mild. The substituted methyl-thio group of each intermediate (126) is acidic because the methylene group has a neighbouring ester group and a sulphur atom, so in the presence of a strong base an anion (127 ; R^1 = Me or Et) is formed. Spontaneous intramolecular cyclisation to the intermediate (128) occurs followed by elimination of a water molecule to give the thienopyrimidine-6-carboxylate (129 ; R^1 = Me or Et, Scheme 4).

Condensations of the primary aminochloropyrimidine (123 k) with one molecular equivalent of ethyl thioglycolate in dimethylformamide at room temperature and in the presence of one molecular equivalent of triethylamine gave a mixture of uncyclised (126 ; NR_2 = NH_2, R^1 = Et) and cyclised (129 f) derivatives, which were isolated by fractional crystallisation. However, when a small amount of dilute potassium hydroxide solution (2N) was added to reactions of the chloropyrimidines (123 a-e) with ethyl thioglycolate, only the cyclised derivatives were obtained (129 a-e).



(124) (125) (123) (126) (127) (128) (129)

	NR_2	R^1		NR_2	R^1
a	$NHMe$	Et	g	$NHMe$	Me
b	$NHEt$	"	h	$N(CH_2)_2O(CH_2)_2$	"
c	$NHCH_2CH{:}CH_2$	"	i	NMe_2	"
d	$NHCH_2Ph$	"	j	$NEtPh$	"
e	$N(CH_2)_4$	"	k	NH_2	"
f	NH_2		l	$N(CH_2)_4$	"

Scheme 4

The efficiency of the cyclisation procedure was clearly dependent on the nature of the base and solvents employed and some effort was made to devise conditions which gave satisfactory yields with a variety of compounds. Although the derivative (129 e) was also obtained when the reaction was carried out in ethanol under reflux conditions using a large excess of sodium carbonate, it was felt that non-homogeneous reactions were less satisfactory. Triethylamine is miscible in alcohols so the use of rather more than two equivalents of this base with one molecular equivalent of methyl thioglycolate was finally adopted for the condensations of the chloropyrimidines (123 a,e,h-k). The reactions were carried out in methanol and under reflux to produce good yields of the cyclised thienopyrimidines (129 g-l, Scheme 4).

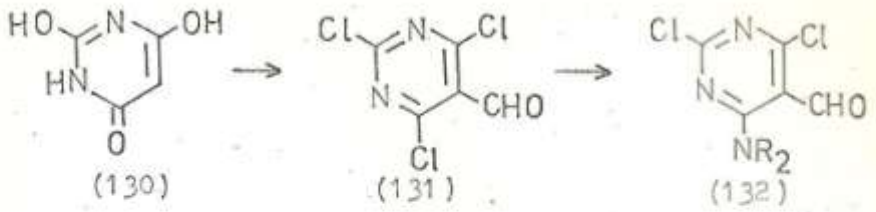
Part 2

The work just described had produced a fairly satisfactory route to a range of 4-substituted thieno-[2,3-d]pyrimidines so it was decided to attempt the preparation of 2,4-disubstituted thieno[2,3-d]pyrimidines by analogous reactions. The required starting material 2,4,6-trichloropyrimidine-5-carbaldehyde (131) had not been described when it was synthesised for this work, but its synthesis has since been published.[199] Both the published method and our method use Vilsmeir formylation and simultaneous introduction of three chlorine atoms into barbituric acid (130), by treatment with phosphoryl

chloride and dimethylformamide (Scheme 5), but the published work-up procedure is much less satisfactory.

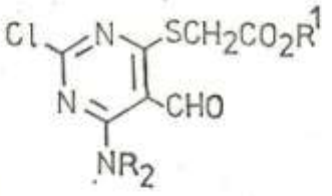
The two chlorine atoms in positions 4 and 6 in the trichloropyrimidine (131) are again in the most favoured positions for activation by the formyl group and the ring nitrogen atoms compared to the chlorine in position 2. Condensations of (131) with one equivalent of a primary or secondary amine in the presence of one equivalent of triethylamine were carried out in dioxan or chloroform and gave the mono substituted 4-amino-2,6-dichloropyrimidine-5-carbaldehydes (132 b-g) (Scheme 5). The conditions were similar to those used for the preparations of the monochloro compounds (123 a-j). 4-Amino-2,6-dichloropyrimidine-5-carbaldehyde (132 a) was prepared by passing ammonia gas through a solution of trichloropyrimidine (131) in benzene at 0°.

The chlorine atoms at positions 2 and 6 in the dichloropyrimidines (132) are active towards further nucleophilic replacement. Under mild conditions such as room temperature and the presence of a little more than two equivalents of methyl thioglycolate and two equivalents of a base in toluene, the intermediate bis-substituted pyrimidine (135 f) could be obtained. This was cyclised in toluene under reflux conditions to the 2,4-substituted-thienopyrimidine (136 f). However, condensation of the pyrimidines (132 b,c) with two molecular equivalents of methyl or ethyl thioglycolate in alcohol or toluene at



(130) (131) (132)

a $NR_2 = NH_2$
b $NR_2 = NHCH_2Ph$
c $NR_2 = N(CH_2Ph)_2$
d $NR_2 = N(CH_2)_4$
e $NR_2 = N(CH_2)_5$
f $NR_2 = N(CH_2)_6$
g $NR_2 = NHC_6H_{11}$



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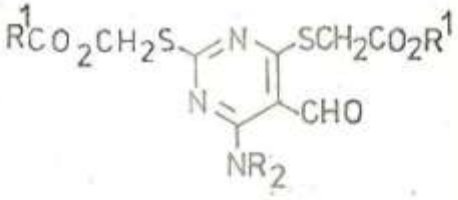

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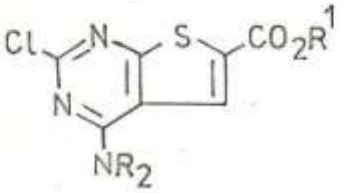

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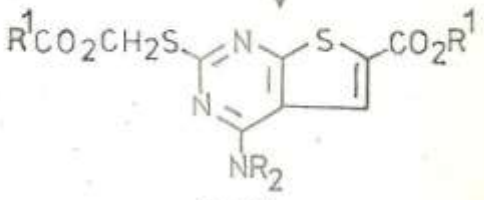


(136)

a $NR_2 = NH_2$, $R^1 = Et$
b $NR_2 = NHCH_2Ph$, $R^1 = Et$
c $NR_2 = N(CH_2Ph)_2$, $R^1 = Et$
d $NR_2 = N(CH_2)_4$, $R^1 = Et$
e $NR_2 = NHCH_2Ph$, $R^1 = Me$
f $NR_2 = N(CH_2Ph)_2$, $R^1 = Me$

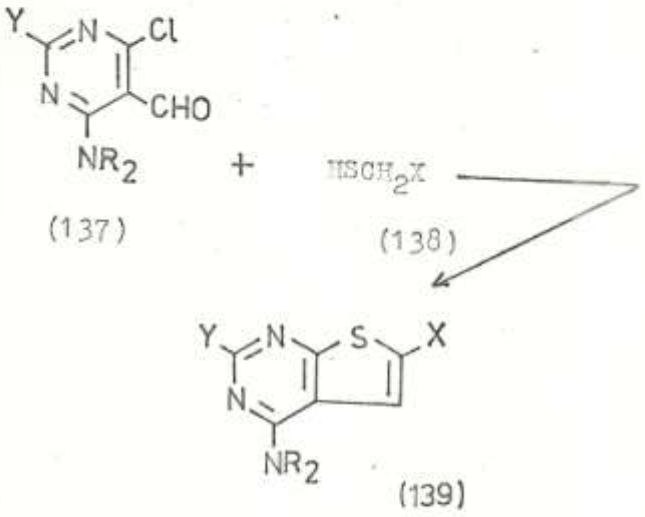
Scheme 5

reflux temperature and in the presence of a little more than two equivalents of triethylamine gave the cyclised derivatives directly (136 b,e and f). When only one equivalent of a thioglycolate was condensed with such a pyrimidine (132) the chlorine atom at position 6 was the more reactive. For example, reactions of dichloropyrimidines (132 a,c,d) with one molecular equivalent of ethyl thioglycolate in dimethylformamide at room temperature and in the presence of one equivalent of triethylamine gave the 6-substituted uncyclised intermediates (133 a, c,d) which were then cyclised to the 2-chlorothieno-pyrimidines (134 a,c,d, Scheme 5).

CHAPTER VII

SYNTHESES OF THIENO[2,3-d]PYRIMIDINES FROM 4-(SUBSTITUTED AMINO)-5-FORMYLPYRIMIDINE-6(1H) THIONES

In principle, the methods described in the previous chapter (VI) could be used for the syntheses of thienopyrimidines (139 ; Y = H or Cl or SCH_2X), with various substituents at position 6 as well as positions 2 and 4, from the chloropyrimidines (137; Y = H or Cl). However, few active methylene compounds with the general formula $HSCH_2X$ (138), where X is an electron withdrawing



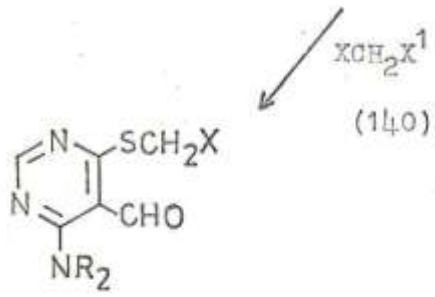
group, are readily available to vary the 6-substituent in (139). Their halogeno analogues XCH_2X^1 (140 ; X = ArCO, CN or CO_2Et, X^1 = Cl or Br) are more available and it was decided to condense these compounds with 4-(substituted amino)-5-formylpyrimidine-6-(1H) thiones (142) to give

the intermediates (143) which were expected to cyclise under basic conditions to the thienopyrimidines (144, Scheme 6) with various substituents at position 6.

Conversion of 4-(substituted amino)-6-chloropyrimidine-5-carbaldehydes (141 a-g) to the pyrimidine-6(1H)thiones (142 a-g) was carried out by treatment with thiourea in 80% aqueous ethanolic solution under reflux. Alternatively, the addition of a methanolic solution of sodium hydrogen sulphide to a methanolic solution of the chloropyrimidine (141 e-g) produced higher yields of the pyrimidine-6-thiones (142 e-g).

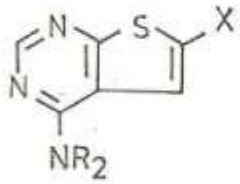
Condensation of the thiones (142 a,b) with phenacyl bromides, ethyl chloroacetate or chloroacetonitrile in methanol and in the presence of an excess of sodium carbonate at room temperature gave the thienopyrimidines [144 a(i-iv),b]. The derivative (144 a v) was isolated when the reaction of (142 a) with chloroacetonitrile was heated under reflux for 15 minutes. Under these more vigorous conditions, hydrolysis of the cyano group occurred. A range of thienopyrimidines (144 c-f) was similarly prepared by condensation of the parent thiones (142 c-f) with phenacyl bromide. When 4-amino-6-chloropyrimidine-5-carbaldehyde (141 g) was heated under reflux with a saturated solution of hydrogen sulphide in acetone for 30 minutes, the product was not the expected aminothione (142 g) but the schiffs base (142 h, Scheme 6). This was condensed with phenacyl bromide in ethanol at reflux temperature to yield the appropriate thienopyrimidine (144 h).

(141) (142)



(140)

(143)



(144)

	NR_2	X		NR_2	X
a(i)	$N(CH_2)_4$	COPh	c	$NHMe$	COPh
(ii)	"	$C_6H_4Br(P)$	d	$NHEt$	"
(iii)	"	CO_2Et	e	NMe_2	"
(iv)	"	CN	f	$N(CH_2)_6$	"
(v)	"	$CONH_2$	g	NH_2	-
b	$NHCH_2Ph$	CO_2Et	h	$NCMe_2$	COPh

Scheme 6

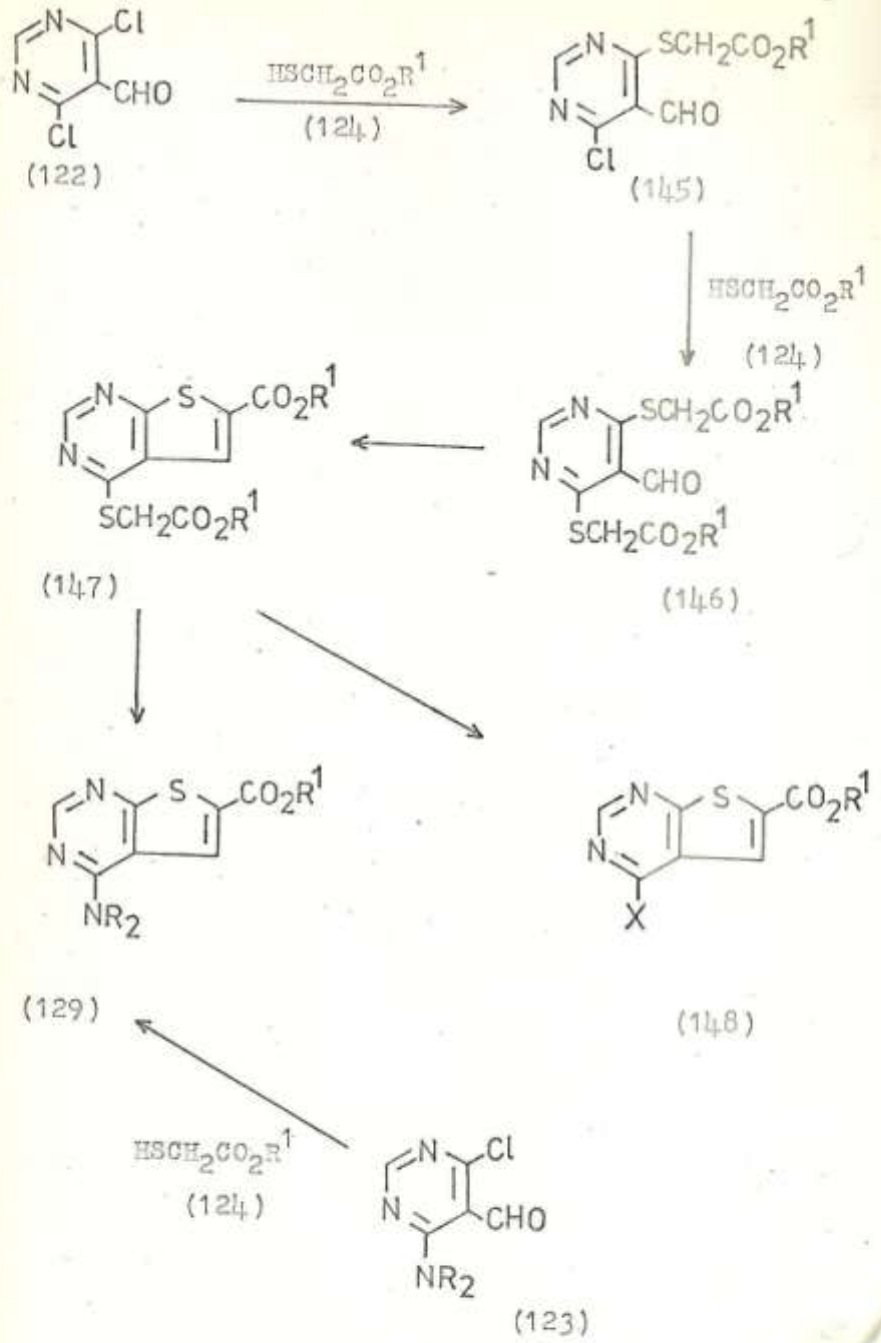
CHAPTER VIII

SYNTHESES OF THIENO[2,3-d]PYRIMIDINES FROM 4,6-DICHLOROPYRIMIDINE-5-CARBALDEHYDES OR 5-CARBONITRILES

The route to thieno[2,3-d]pyrimidines explored in Chapter VI was suitable for synthesising small quantities of a variety of compounds, but was rather unsatisfactory in some ways. The initial step involved replacing one of two identical chlorine atoms with another group. This worked fairly well when the substituent introduced was an amino, alkylamino or saturated cyclic amino group but it was difficult to introduce some other groups such as a single arylamino, hydroxy or methoxy group cleanly and in good yield. Furthermore, it meant doing a different initial step for every different thienopyrimidine required.

It is known that the methylthio and other substituted thio groups work well as leaving groups in nucleophilic substitution reactions[17,113,201] so a different approach to the problem, involving a common first step for a group of thienopyrimidines was possible (Scheme 7).

Condensation of the dichloropyrimidine (122) with an excess of an alkyl thioglycolate (124 ; R^1 = Me or Et), under basic conditions, gave a thienopyrimidine (147 ; R^1 = Me or Et). Replacement of both chlorine atoms gave the bis-alkoxycarbonylmethylthio intermediate (146)


Cl
N
CHO
Cl
(122)
HSCH2CO2R1
(124)
SCH2CO2R1
CHO
Cl
(145)
HSCH2CO2R1
(124)
SCH2CO2R1
CHO
SCH2CO2R1
(146)
S
CO2R1
N
SCH2CO2R1
(147)
NR2
(129)
X
(148)
HSCH2CO2R1
(124)
Cl
CHO
NR2
(123)

Scheme 7

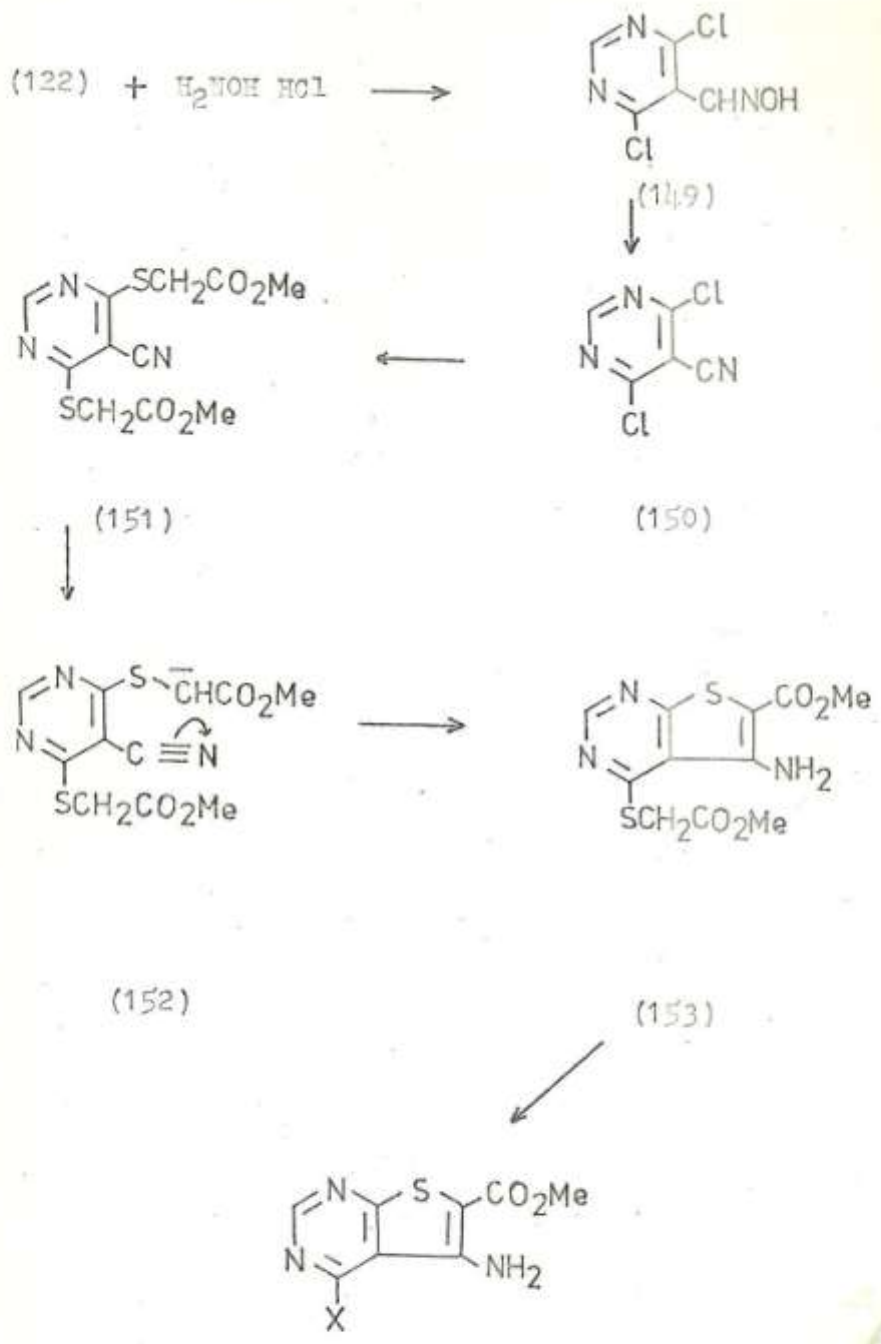
which could be isolated and cyclised in various solvents to give the thienopyrimidines (147 ; R^1 = Me or Et, Scheme 7). This method provided a very good route to a thienopyrimidine (147) with a group at position 4 replaceable by various nucleophiles to give a wide range of 4-substituted derivatives (148) (see Chapter X). For example, reaction of the thienopyrimidine (147 ; R^1 = Me or Et) with various amines gave 4-(substituted amino)- derivatives (129) some of which had already been prepared by condensation of the aminochloropyrimidines (123) with alkyl thioglycolates (Chapter VI).

Various conditions were tried for the synthesis of the 4-alkoxycarbonylmethylthio thienopyrimidines (147). For example, condensation of the dichloropyrimidine (122) with a little more than two molecular equivalents of methyl thioglycolate (124 ; R^1 = Me) was carried out at room temperature in methanol or in dioxan using an excess of sodium carbonate or triethylamine as a base to give the uncyclised 4,6-bis-(methoxycarbonylmethylthio)-pyrimidine-5-carbaldehyde (146 ; R^1 = Me) in good yield. Cyclisation of this intermediate (146) was then carried out in toluene at reflux temperature and in the presence of a small amount of triethylamine as a catalyst to give methyl 4-methoxycarbonylmethylthiothienopyrimidine-6-carboxylate (147 ; R^1 = Me). Evidently, formation of the uncyclised intermediate (146) proceeds quickly and at room temperature, but the intramolecular cyclisation requires a higher temperature. This was also shown when

the condensations of dichloropyrimidine (122) with a little more than two equivalents of methyl or ethyl thioglycolate were allowed to proceed in methanol or ethanol at room temperature, using an excess of sodium carbonate as a base, as described above except that the reaction mixtures were heated to remove the solvent at the end of the reaction; the cyclised derivative (147 ; R^1 = Me or Et) were isolated directly and in good yields.

The idea of replacing both chlorine atoms of a dichloropyrimidine by alkoxycarbonylmethylthio groups, allowing one of these groups to form the thiophen ring and then using the other as a leaving group in nucleophilic substitution had worked well. However, one of the long term aims of this project is to provide tricyclic compounds containing the thienopyrimidine ring system so it was desirable to have the thiophen ring suitably substituted for building on the third ring. This was made possible by using 4,6-dichloropyrimidine-5-carbonitrile.

4,6-Dichloropyrimidine-5-carbaldehyde (122) was converted into the 5-carbonitrile (150, Scheme 8) via its oxime (149) which was dehydrated by thionyl chloride.[193,200] Condensation of dichloropyrimidine-5-carbonitrile (150) with an excess of methyl thioglycolate was tried under various conditions and in different solvents. When the condensation was carried out in diethyl ether at room temperature using an excess of sodium carbonate as a base, the uncyclised 4,6-bis-(methoxycarbonylmethylthio)-pyrimidine-5-carbonitrile (151, Scheme 8) was isolated in

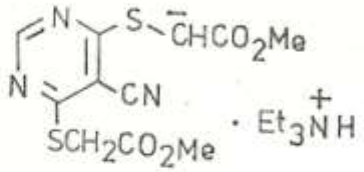

(122) + H_2NOH HCl
CHNOH
(149)
SCH_2CO_2Me
CN
SCH_2CO_2Me
(151)
(150)
$CHCO_2Me$
CO_2Me
NH_2
(152)
(153)
X
(154)

Scheme 8

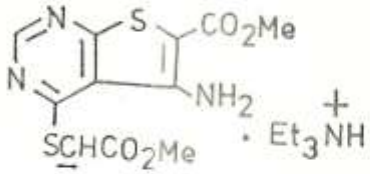
good yield. The cyclisation of this was carried out in toluene at reflux temperature and in the presence of a small amount of triethylamine as a catalyst to give the 5-amino-4-methoxycarbonylmethylthiothienopyrimidine (153) in reasonable yield (70%). However, when the condensation of dichloropyrimidine (150) with a little more than two equivalents of methyl thioglycolate was allowed to proceed in methanol at room temperature and the reaction mixture was then heated to remove methanol, an unexpected 4-methoxythienopyrimidine (154 ; X = OMe) was isolated. This may have been due to generation of methoxide anions in methanol by the excess of sodium carbonate. Nucleophilic substitution of the 4-methoxycarbonylmethylthio group by methoxide anions may have occurred before or after cyclisation to the thienopyrimidine (153, Scheme 8). To overcome this problem, condensation of the dichloropyrimidine (150) with an excess of methyl thioglycolate was done in toluene at room temperature using an excess of triethylamine as a basic catalyst. The reaction mixture was then heated under reflux, filtered while hot and cooled to give the cyclised 5-aminothienopyrimidine directly (153).

The yield of product (153) following the use of triethylamine as a base and toluene as a solvent for the condensation and cyclisation was not considerably improved (80%). This could have been due to filtration of triethylammonium salts (155) or (156) from the hot reaction mixture alongside triethylamine hydrochloride

which is formed as a result of the nucleophilic substitution of both chlorine atoms. However, the advantage of synthesising the product (153) by one step from the dichloropyrimidine (150) outweighed the small loss in the yield.

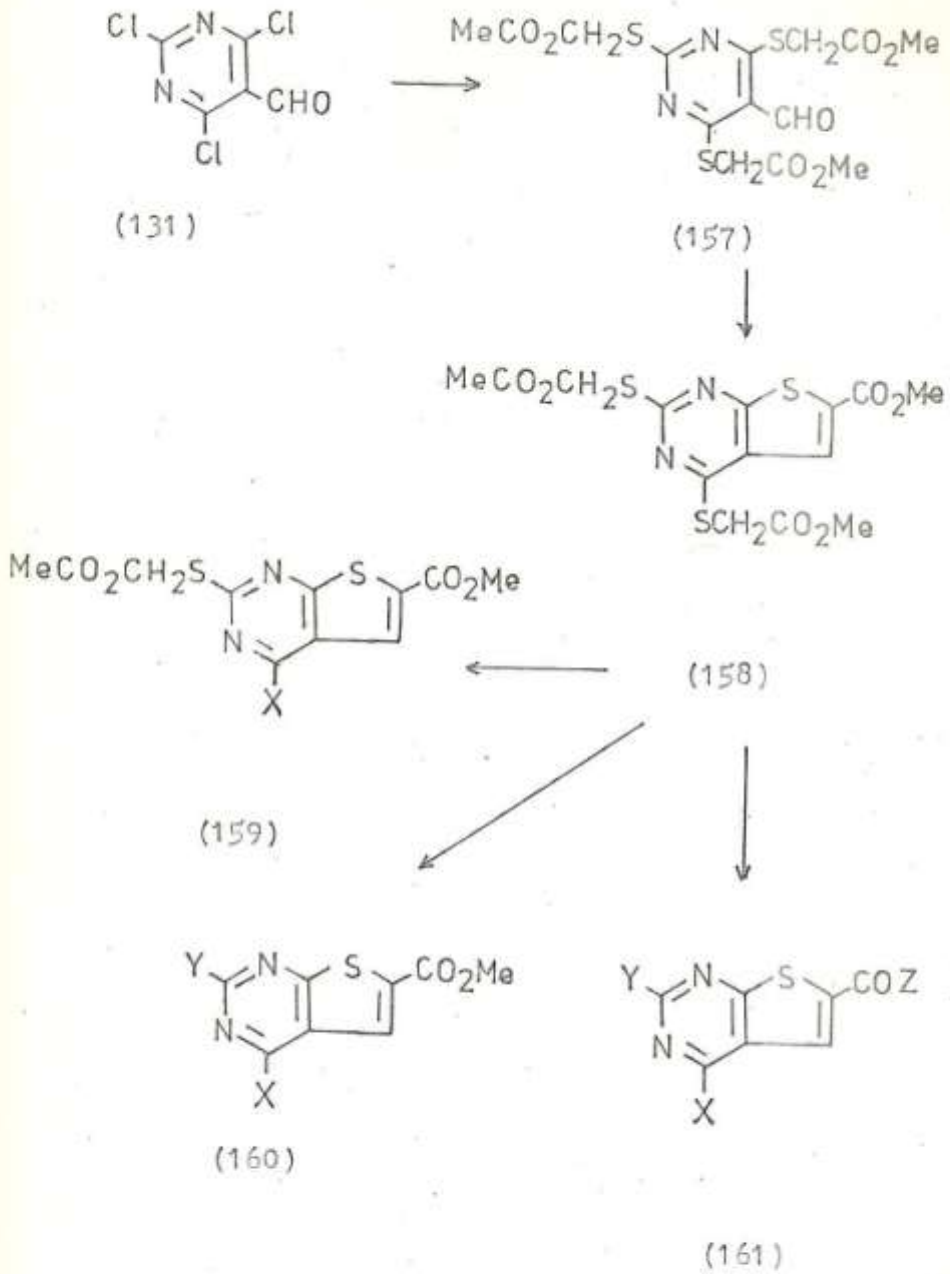


(155)



(156)

The syntheses of 4-substituted thienopyrimidines and their 5-amino analogues from dichloropyrimidine-5-carbaldehyde and 5-carbonitrile were very successful in providing starting materials (147) and (153) which could be used for the preparation of any desired 2-unsubstituted thienopyrimidine (Chapter X). However, it was clear that the synthesis of a similar thienopyrimidine (158, Scheme 9) with groups at positions 2 and 4 easily replaced by nucleophiles would provide a wider range of thienopyrimidines (159) to (161) in which the 2- and 4-substituents may be the same or different (Chapter X).



(131)

(157)

(158)

(159)

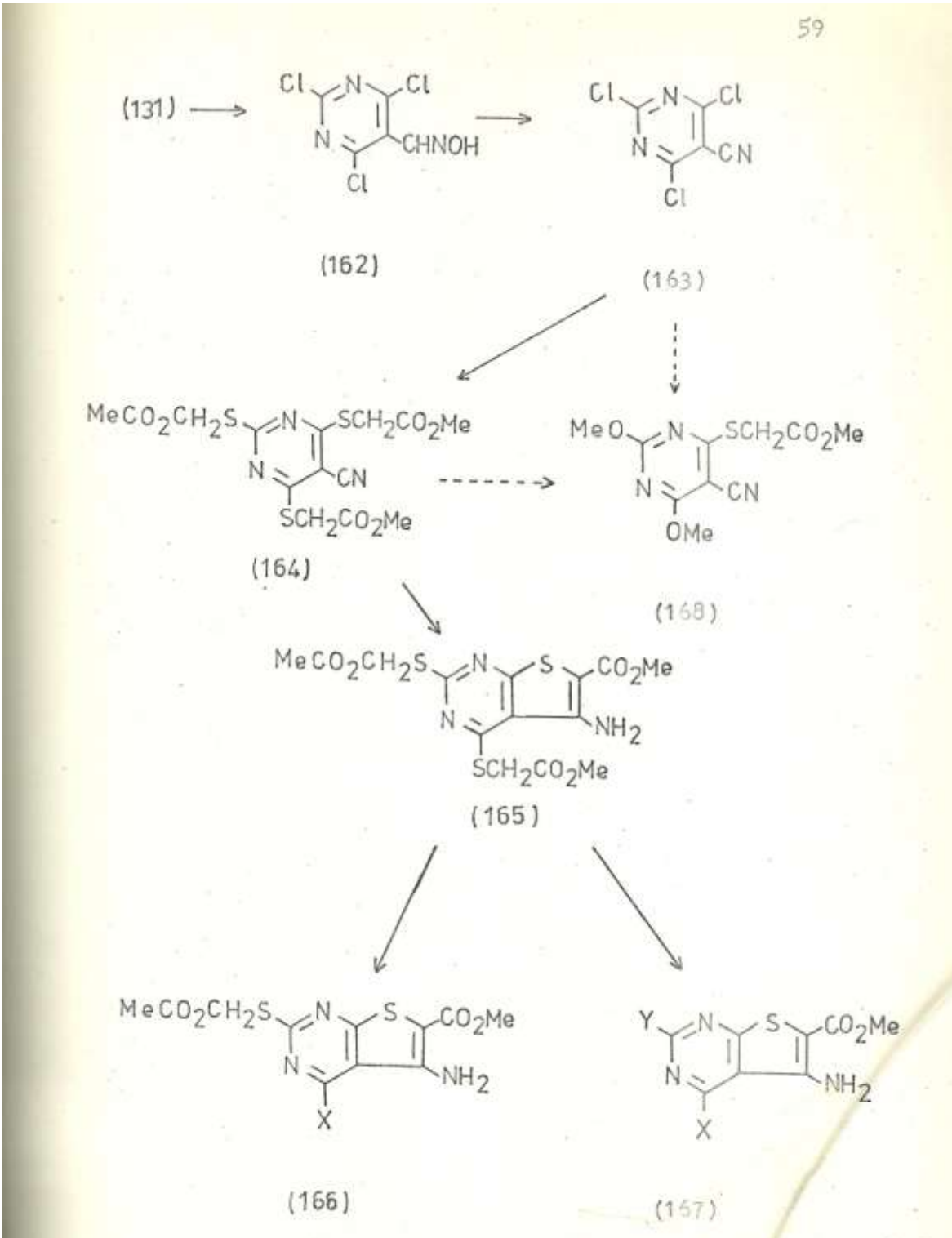
(160)

(161)

Scheme 9

Such a thienopyrimidine (158) was prepared by reaction of the trichloropyrimidine (131) with a little more than three molecular equivalents of methyl thioglycolate in toluene using an excess of triethylamine as a base and catalyst for the condensation and cyclisation respectively. Replacement of the three chlorine atoms gives the 2,4,6-tris-(methoxycarbonylmethylthio)pyrimidine-5-carbaldehyde (157) which easily cyclises to the 2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine (158, Scheme 9). The reaction was allowed to proceed at room temperature for some time before the mixture was heated under reflux, filtered while hot, and cooled to give the crystalline product directly (158). The yield of thienopyrimidine (158) was not as good as expected (75%). This may also be due to the filtration of salts similar in nature to those described earlier (155) and (156) from the hot reaction mixture.

Replacements of all three chlorine atoms in the trichloropyrimidine (131) by methoxycarbonylmethylthio groups; allowing one of these to form the thiophen ring and using the other two groups as leaving groups in nucleophilic substitution had also worked well. Unfortunately, the empty 5-position in such a thienopyrimidine prevents the build up of a third ring onto the thiophen ring. However, similar use of trichloropyrimidine-5-carbonitrile promised to provide a thienopyrimidine (165, Scheme 10) with the thiophen suitably substituted for building on a further ring.


(131)
Cl
N
Cl
CHNOH
Cl
(162)
Cl
N
Cl
CN
Cl
(163)
MeCO2CH2S
N
SCH2CO2Me
N
CN
SCH2CO2Me
(164)
MeO
N
SCH2CO2Me
N
CN
OMe
(168)
MeCO2CH2S
N
S
CO2Me
N
NH2
SCH2CO2Me
(165)
MeCO2CH2S
N
S
CO2Me
N
NH2
X
(166)
Y
N
S
CO2Me
N
NH2
X
(167)

Scheme 10

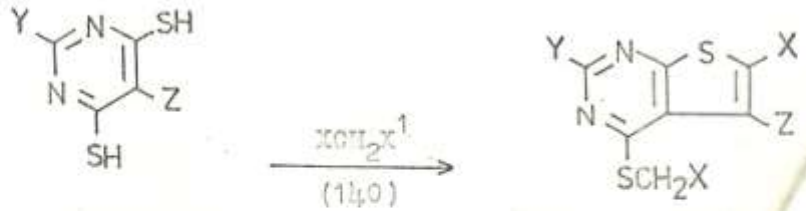
2,4,6-Trichloropyrimidine-5-carbaldehyde (131) was converted into the 5-carbonitrile (163, Scheme 10) via its oxime (162) which was dehydrated by thionyl chloride. Condensation of trichloropyrimidine-5-carbonitrile (163) with an excess of methyl thioglycolate was also tried in different solvents and under various conditions. The results of these trials were somewhat similar to those obtained from the reaction of its dichloro analogue (150) with an excess of methyl thioglycolate which were discussed earlier. For example, when the reaction of trichloropyrimidine (163) with a little more than three molecular equivalents of methyl thioglycolate was carried out in diethyl ether at room temperature using an excess of sodium carbonate, the 2,4,6-tris-(methoxycarbonylmethylthio)pyrimidine-5-carbonitrile (164, Scheme 10) was isolated in excellent yield (75%). Cyclisation of this was carried out in toluene at reflux temperature and in the presence of triethylamine as a catalyst to give the 5-amino-2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine (165, Scheme 10). However, when the reaction was repeated in methanol and the condensation was allowed to proceed for two days at room temperature, using sodium carbonate as a base, the unexpected 4-methoxy derivative (166 ; X = OMe) was isolated. Similarly isolated were the unexpected cyclised (167 ; X, Y = OMe) and uncyclised (168) 2,4-dimethoxy derivatives (Scheme 10). To avoid such undesired replacement of the 2- and(or) 4-methoxycarbonylmethylthio groups the condensation and

cyclisation were carried out in toluene at reflux temperature using an excess of triethylamine as basic catalyst to give the cyclised product (165) directly in crystalline form. The convenience of this method compensated for the small loss in the yield, possibly due to the formation of salts similar to those described earlier (p.55).

CHAPTER IX

SYNTHESES OF THIENO[2,3-d]PYRIMIDINES FROM POLYMERCAPTOPYRIMIDINE-5-CARBONITRILES AND 5-CARBALDEHYDE

It has already been pointed out that active methylene compounds containing a substituted methythio group are not very readily available (p.47) so it was not easy to extend the syntheses described in the previous chapter to the preparation of thienopyrimidines with a 6-substituents other than alkoxycarbonyl. However, the principle of preparing a pyrimidine with two or more substituted methylthio groups and using one to provide a thiophen ring and the other(s) as a leaving group or groups was developed further by condensing di- or tri-mercaptopyrimidines (169 ; Y = H or SH, Z = CN or CHO) with the readily available halogeno compounds (140 ; X = CO_2Me, CO_2Et, COMe, COAr, $CONH_2$ or CN; X^1 = Cl or Br) to produce the desired thienopyrimidines (170 ; Y = H or SCH_2X, Z = NH_2 or H).

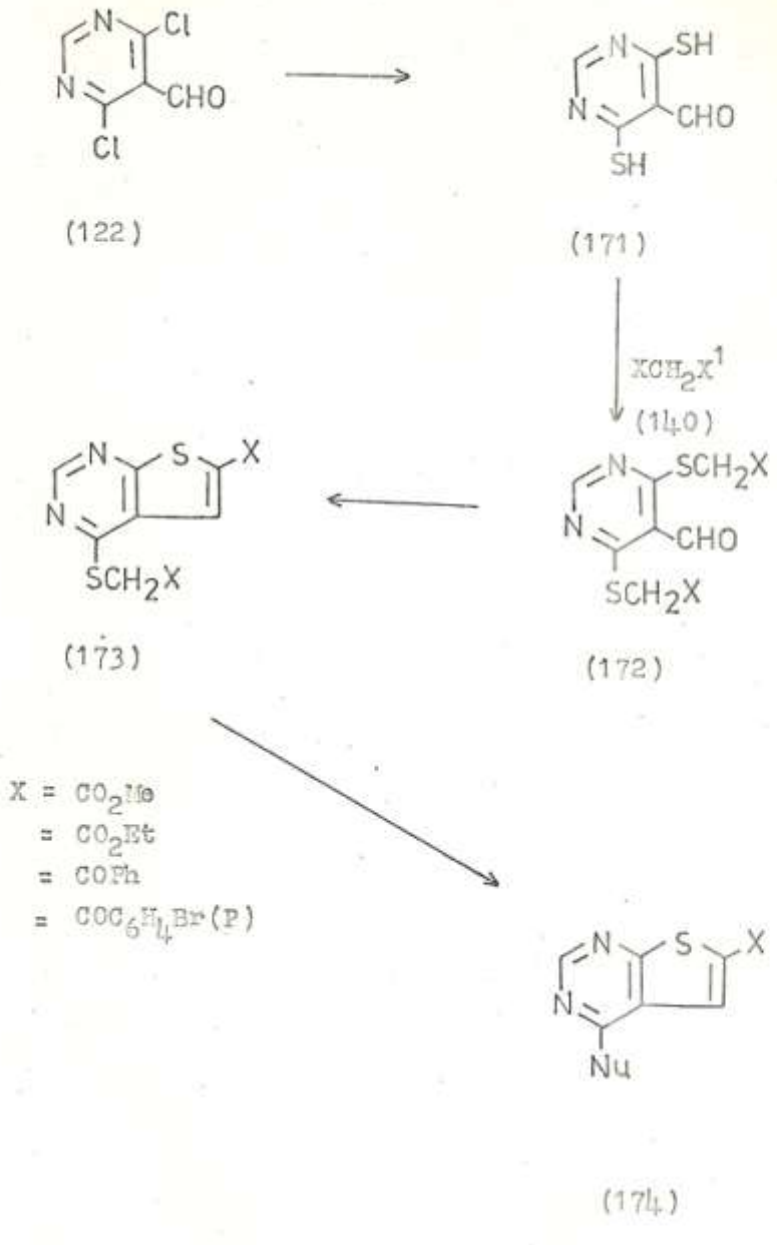


(169) (170)

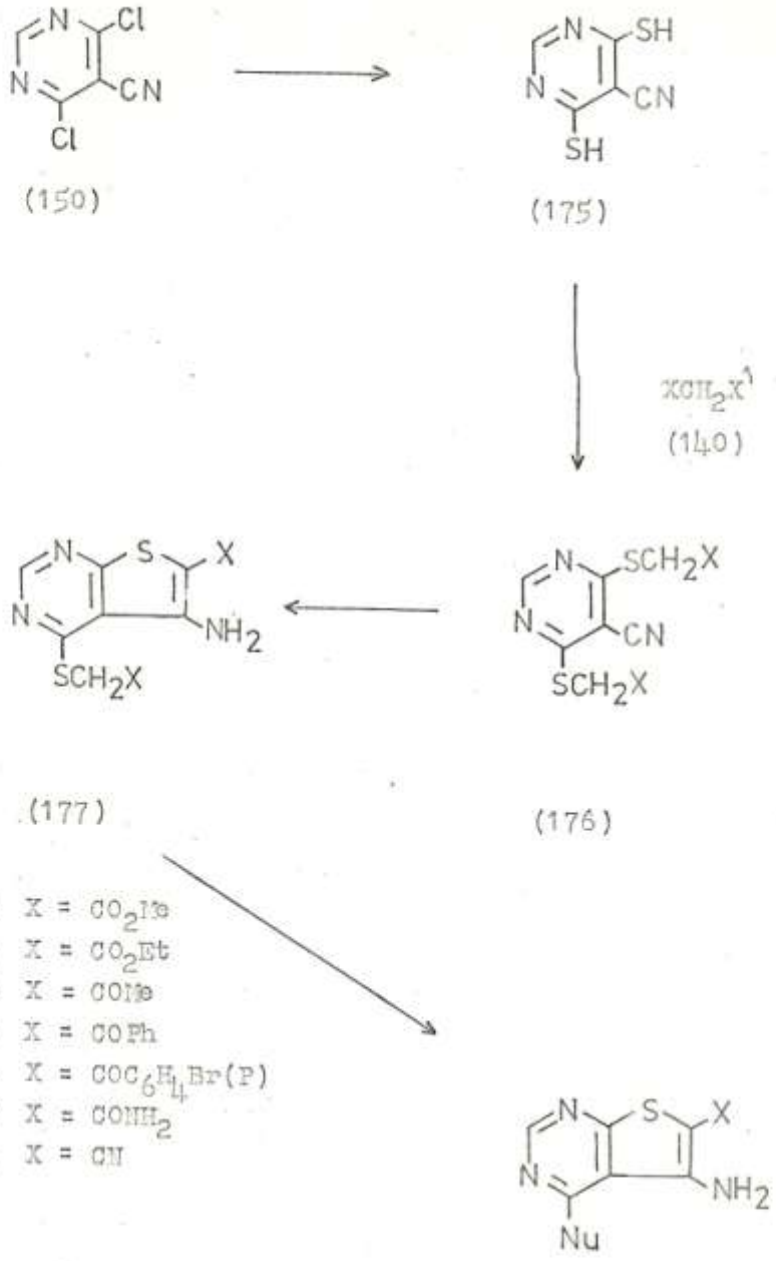
Conversion of 4,6-dichloropyrimidine-5-carbaldehyde (122) to the 4,6-dimercapto compound (171) was carried out by treatment with thiourea in 80% aqueous ethanolic solution under reflux. Alternatively, the addition of a methanolic solution of sodium hydrogen sulphide to the methanolic solution of the dichloropyrimidine (122) produced a higher yield of the 4,6-dimercapto derivative (171).

Reactions of 4,6-dimercaptopyrimidine-5-carbaldehyde (171) with alkyl chloroacetates or phenacyl bromides in methanol at room temperature, using an excess of triethylamine gave the thienopyrimidines [173; X=CO_2Me, CO_2Et, COPh or $COC_6H_4Br_{(p)}$]. (Scheme 11)

Condensation of the dimercaptopyrimidine (171) with halogeno compounds (140) worked fairly well giving good yields of thienopyrimidines (173) with various substituents at positions 4 and 6. It was therefore decided to condense the 4,6-dimercaptopyrimidine-5-carbonitrile (175) with such halogeno compounds (140) to produce thienopyrimidines (177) (Scheme 12) with groups at position 4 replaceable by nucleophiles to give (178). Such thienopyrimidines (177) and (178) could be considered as precursors of tricyclic compounds containing the thienopyrimidine system, since the primary amino group at position 5 and a suitable keto or ester group at position 6 provide the basis for building a third ring around the thiophen ring.


Cl
N
CHO
Cl
SH
SH
(122)
(171)
XCH_2X^1
(140)
SCH_2X
SCH_2X
S
X
SCH_2X
(173)
(172)
X = CO_2Me
= CO_2Et
= COPh
= $COC_6H_4Br(P)$
Nu
(174)

Scheme 11


(150)
(175)
XCH_2X^1
(140)
(177)
(176)
a X = CO_2Me
b X = CO_2Et
c X = COMe
d X = COPh
e X = $COC_6H_4Br(P)$
f X = $CONH_2$
G X = CN
(178)

Scheme 12

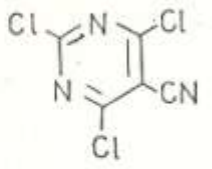
Conversion of dichloropyrimidine-5-carbonitrile (150) to the dimercapto derivative (175) was carried out under the same conditions used for the preparation of the 5-carbaldehyde analogue (171) described earlier. The reactions of dimercaptopyrimidine-5-carbonitrile (175) with methyl or ethyl chloroacetate, chloroacetone, phenacyl bromides, chloroacetamide or chloroacetonitrile were carried out in methanol at room temperature, using an excess of triethylamine as a base, to give the 5-amino-thienopyrimidines (177) (Scheme 12).

The formation of 4,6-bis-(substituted methylthio)-pyrimidine intermediates (172) and (176) and their cyclisation to the appropriate thienopyrimidines (173 and 177 respectively) in the presence of an excess of triethylamine proceeded quickly. The time taken for the cyclised products (173) and (177) to precipitate from the reaction mixtures was less than five minutes. Higher yields of thienopyrimidines (173 and 177 ; X = CO_2Me or CO_2Et) were obtained using this method than those obtained by the condensations of dichloropyrimidines (122) and (150) with an excess of alkyl thioglycolates (124 ; R^1 = Me or Et) in toluene. The improved yields may be due to the expected higher solubilities of triethyl-ammonium salts, similar to (155) and (156), in methanol than in toluene, (p.55).

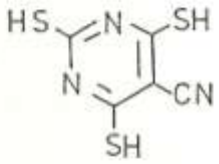
Reactions of mercaptopyrimidines (171 and 175) with halogeno compounds (140) were successful in producing a wide range of thienopyrimidines (173 and 177) in good yields. This condensation was extended further to include 2,4,6-trimercaptopyrimidine-5-carbonitrile (179) which is expected to give the fully substituted thienopyrimidine (181) with groups at position 2 and 4 which may undergo successive nucleophilic substitution, to give 2- and(or) 4-substituted derivatives (see Chapter X). The primary amino group at position 5 in the thienopyrimidine (181) would provide thebasis for the syntheses of tricyclic compounds containing the thienopyrimidine system.

Conversion of 2,4,6-trichloropyrimidine-5-carbonitrile (163) to the 2,4,6-trimercapto analogue (179) was attempted by treatment with thiourea in 80% aqueous ethanolic solution under reflux. Elemental analyses of the product were unsatisfactory but it reacted with a little more than three equivalents of methyl chloroacetate or phenacyl bromide in methanol, using an excess of triethylamine, to give the thienopyrimidines (181; X = CO_2Me or COPh) presumably via the condensed uncyclised derivatives (180) (Scheme 13). Such a thienopyrimidine (181; X = CO_2Me) had already been synthesised by reaction of the trichloropyrimidine (163) with an excess of methyl thioglycolate (Chapter VIII).

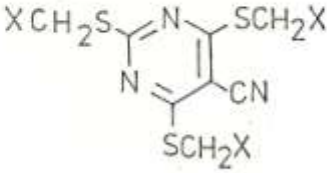
Conversion of 2,4,6-trichloropyrimidine-5-carbaldehyde (131) to the trimercapto compound (182; Scheme 13) was



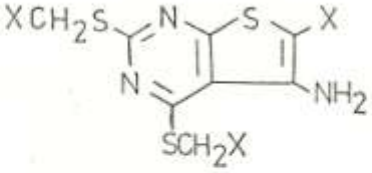
(153)



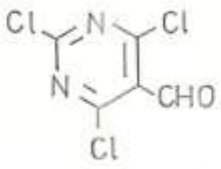
(179)



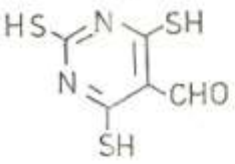
(180)



(181)



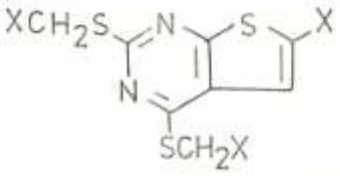
(131)



(182)

XCH_2X^1

(140)



(183)

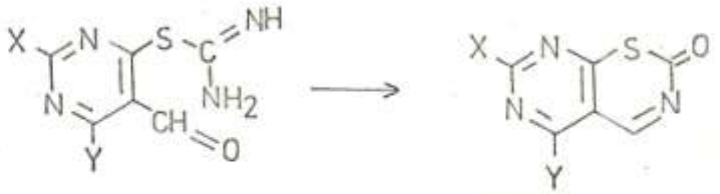
(183; X = CO_2Me = 158)

Scheme 13

attempted under conditions similar to those used for the preparation of the nitrile (179). Though the product of this conversion was soluble in methanol in the presence of an excess of triethylamine, its reaction with three molecular equivalents of methyl chloroacetate gave an unknown product different from the expected thieno-pyrimidine (183; X = CO_2Me) which had previously been prepared from the trichloro pyrimidine and methyl thioglycolate (158; Chapter VIII).

The unsatisfactory elemental analyses obtained for the trimercaptocyanopyrimidine (179) may be due to the presence of an equal amount of urea which crystallised out with the trimercaptopyrimidine.

Sufficient time was not available to look into the factors affecting the conversion of the trichloro-formylpyrimidine (131) to the trimercapto analogue (182). However, formation of a thiouronium derivative (184) which may undergo cyclisation and loss of a water molecule followed by hydrolysis of the 7-imino group to give the pyrimidothiazine (185) was suspected.



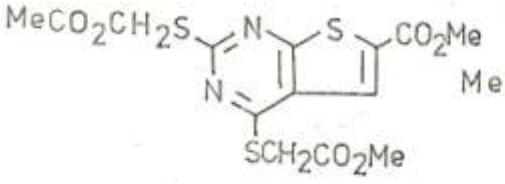
(184) (185)

CHAPTER X

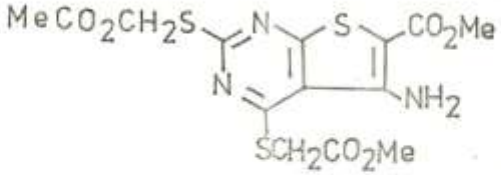
PROPERTIES OF SOME THIENO[2,3-d]PYRIMIDINES

The principle aim of this research was to provide suitable and convenient routes for the syntheses of thieno[2,3-d]pyrimidine derivatives with similar or different substituents in positions 2, 4 and 6. This aim was achieved through the syntheses discussed in the previous chapters VIII and IX.

The routes involving bis- or tris-(substituted-methylthio)pyrimidine-5-carbaldehydes or carbonitriles looked like being very productive if controlled replacement of the substituents in the resulting thieno-pyrimidines could be achieved. In the more complex esters (158) and (165) nucleophilic attack is likely at five different positions, namely the carbonyl carbon



(158)

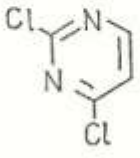


(165)

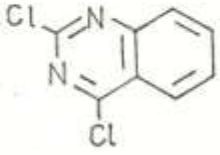
atoms of each of the three ester groups and the 2 and 4 positions of the pyrimidine ring. It was anticipated that the methoxycarbonylmethylthio groups would be replaced as complete units, but their relative reactivities

were uncertain. It was clearly necessary to investigate the nucleophilic substitution reactions of the compounds in some detail.

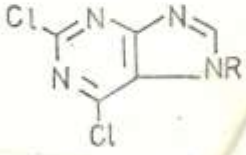
It was known that the alkylthio and other substituted thio groups work well as leaving groups in nucleophilic substitution reactions.[201-214] The groups concerned have usually been methylthio, ethylthio, benzylthio or phenylthio but the carboxy- or ethoxy-carbonylmethylthio groups have also been involved in displacements.[221,222] The reactivities of the substituted thio groups are often comparable with or greater than that of a similarly situated chlorine atom. When the substituents in positions 2 and 4 of pyrimidine and the fused pyrimidine systems (e.g. a, b and c) are chlorine atoms, the one at position 2 will activate the chlorine atom at position 4 more than the reverse due to differences in their conjugative and inductive interactions with the ring.[202] Therefore, only mild conditions may be required for the nucleophilic replacement of the chlorine atom in position 4 compared with more vigorous conditions required for the replacement of the chlorine atom in position 2.[203-214]



(a)



(b)

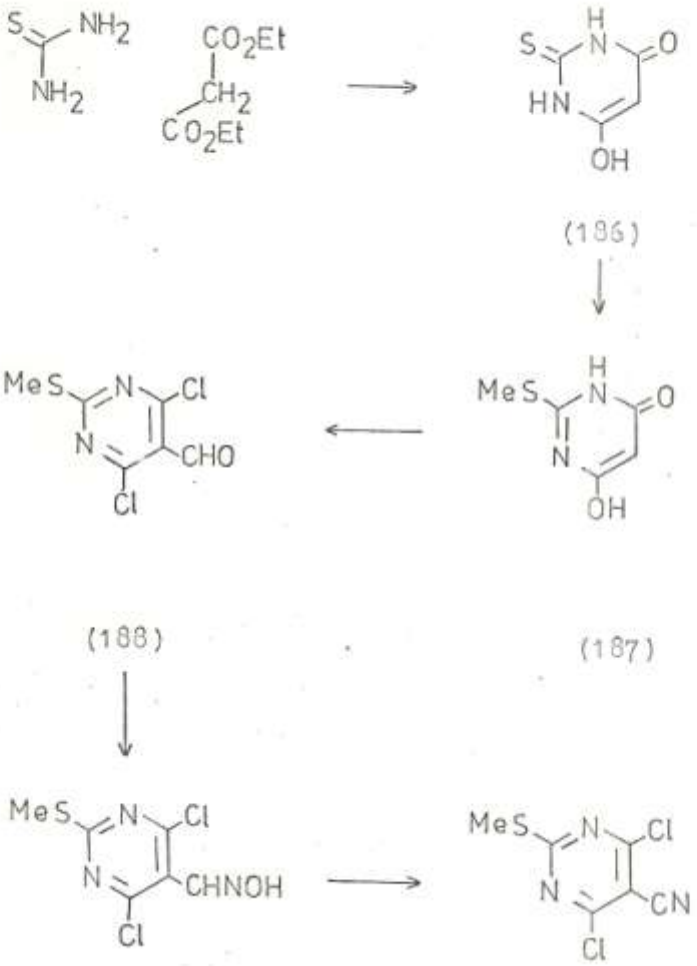


(c)

One of the methoxycarbonylmethylthio groups in position 2 and 4 in the thienopyrimidines (158 and 165) was definitely more reactive towards nucleophiles because a single product in which only one of the groups had been replaced could readily be isolated. In order to show which groups had been displaced it was necessary to synthesise thienopyrimidines in which the substituents at positions 2 and 4 were known unambiguously. It was decided to prepare a pyrimidine derivative which would act as a precursor for the syntheses of such thienopyrimidines.

Condensation of thiourea with diethylmalonate in an ethanolic solution of sodium ethoxide produced 4,6-dihydroxy-2-mercaptopyrimidine[218] (186) which was methylated using dimethyl sulphate in alkaline solution to give 4,6-dihydroxy-2-methylthiopyrimidine[219] (187). Vilsmeir formylation and simultaneous introduction of two chlorine atoms in dimethylformamide and phosphoryl chloride yielded 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde[113] (188) (Scheme 14).

Conversion of the pyrimidine-5-carbaldehyde to its oxime (189) was carried out in glacial acetic acid using hydroxylamine hydrochloride, and dehydration of the oxime in thionyl chloride gave the 5-carbonitrile (190) (Scheme 14).



(186)

(188)

(187)

(189)

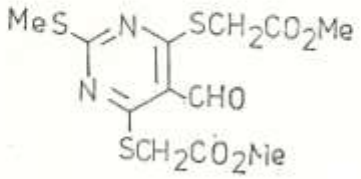
(190)

Scheme 14

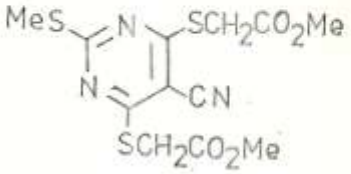
Reaction of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (188) with a little more than two equivalents of methyl thioglycolate in toluene, using an excess of triethylamine as a base, gave the 4,6-bis substituted derivative (191) at room temperature. Cyclisation of this to the thienopyrimidine (192) was carried out under reflux (Scheme 15). Similarly prepared was the 5-aminothienopyrimidine (195) directly from the pyrimidine-5-carbonitrile (190), presumably through the bis substituted derivative (194).

The methylthio group in the thienopyrimidine (192) is placed unambiguously in position 2. Reaction of the bis(methoxycarbonylmethylthio)thienopyrimidine (158) with a methanolic solution of sodium methyl mercaptide for 10 minutes at room temperature gave a methylthio derivative (159a) which was different from its structural isomer (192) and was therefore a 4-methylthio derivative. Alternatively, reaction of the thienopyrimidine (158) with a methanolic solution of sodium hydrogen sulphide at room temperature gave a thiol (159b) which was methylated using methyl iodide to give a product (159a) identical with that prepared above. Once again the 4-substituent was the more reactive. However, when reaction of the thienopyrimidine (158) with a methanolic solution of sodium methyl mercaptide was allowed to proceed for one hour at room temperature, replacement of both 2, and 4-substituents occurred and the bis-methylthio derivative (160a) was isolated (Scheme 16). The

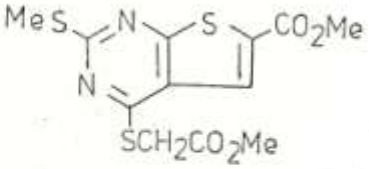
(188)



(190)



(191)



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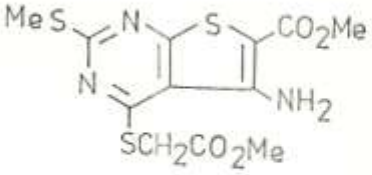
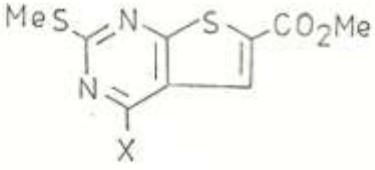
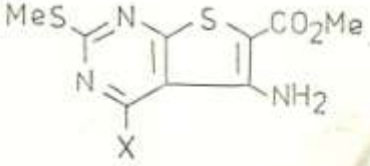


(192)



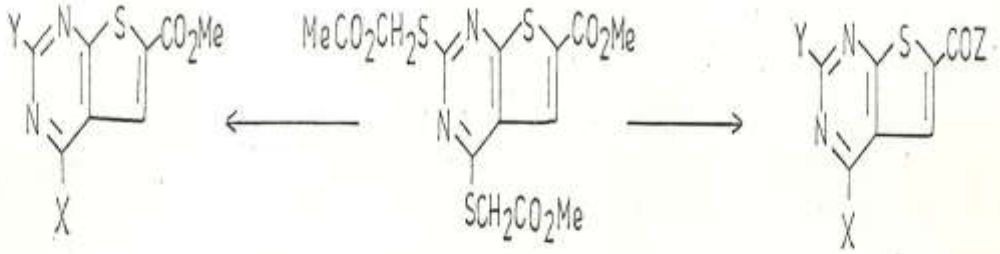
(195)



(193)

(196)

Schema 15



(160)

(158)

(161)

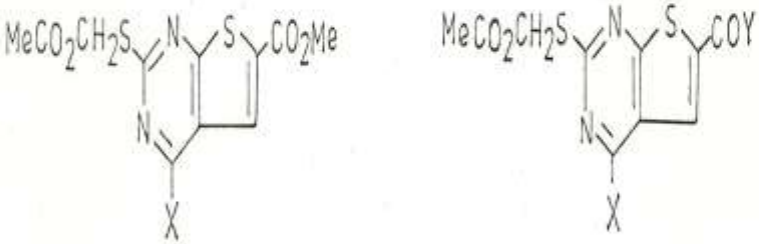
a X = Y = SMe

b X = $N(CH_2)_5$, Y = SMe

c X = Y = $N(CH_2)_4$

a X Y Z $N(CH_2)_4$

b X Y Z OEt



(159)

(197)

a X = SH

b X = NH

c X = $N(CH_2)_5$

d X = $N(CH_2)_2O(CH_2)_2$

e X = OMe

a X = SH, Y = $N(CH_2)_5$

b X = Y = $N(CH_2)_5$

c X = Y = $N(CH_2)_2O(CH_2)_2$

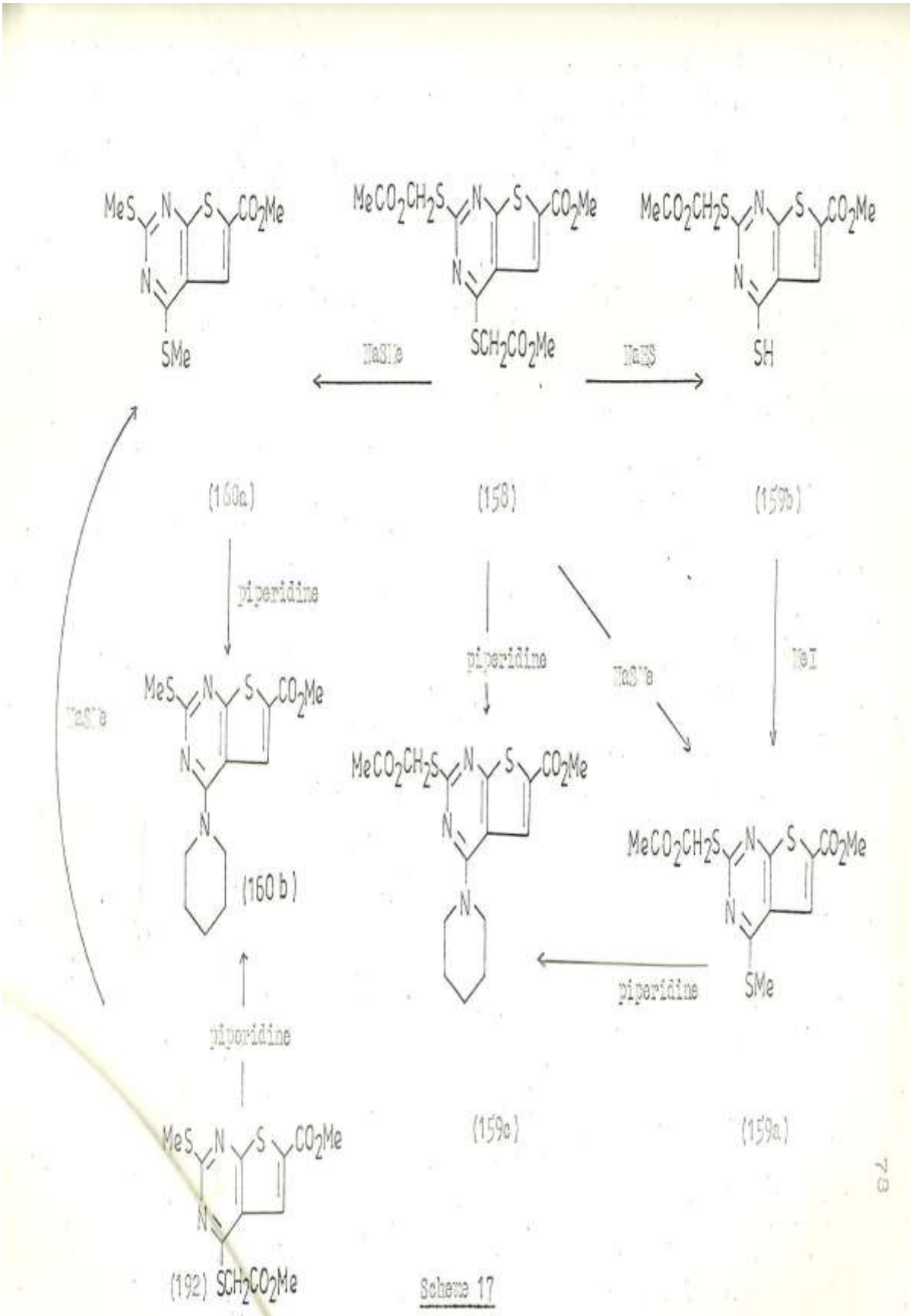
d X = Y = $NHCH_2Ph$

e X = Y = $NHNH_2$

Schema 16

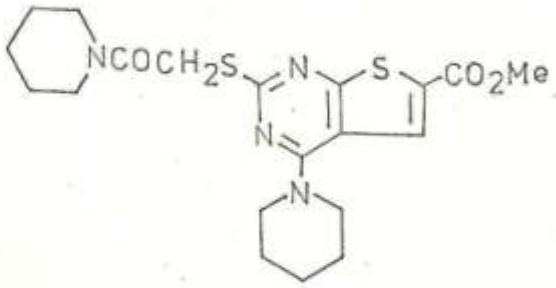
latter reacted with neat piperidine at room temperature to yield a thienopyrimidine (160b) identical with one prepared by condensation of the 2-methylthio derivative (192) with piperidine under similar conditions. Similarly, the bis(methoxycarbonylmethylthio)thieno-pyrimidines (158) reacted with piperidine to give a monopiperidino compound identical with that prepared by the condensation of the 4-methylthiothienopyrimidine (159a) with piperidine. Piperidine therefore had also reacted preferentially at position 4 of the thieno-pyrimidines (158 and 159a) to give the expected product (159c). Since three different nucleophiles SMe, SH and piperidine had all reacted preferentially at position 4 of the bis(methoxycarbonylmethylthio)thienopyrimidine (158) it was considered safe to assume that in all reactions of the 2,4-bis substituted methylthio-pyrimidines the 4-substituent is replaced first just as the 4-chlorine atom is replaced first in corresponding dichloro compounds. All the above reactions are summarised in Scheme 17 and physical data of some of the derivatives are shown in Table 5 (page 102).

The thienopyrimidine (158) has three important active sites for nucleophilic substitution reactions although it is clear from the previous paragraphs that position 4 is the most reactive. It was expected that once the substituent at position 4 was no longer reactive towards nucleophiles, the activity of a group at position

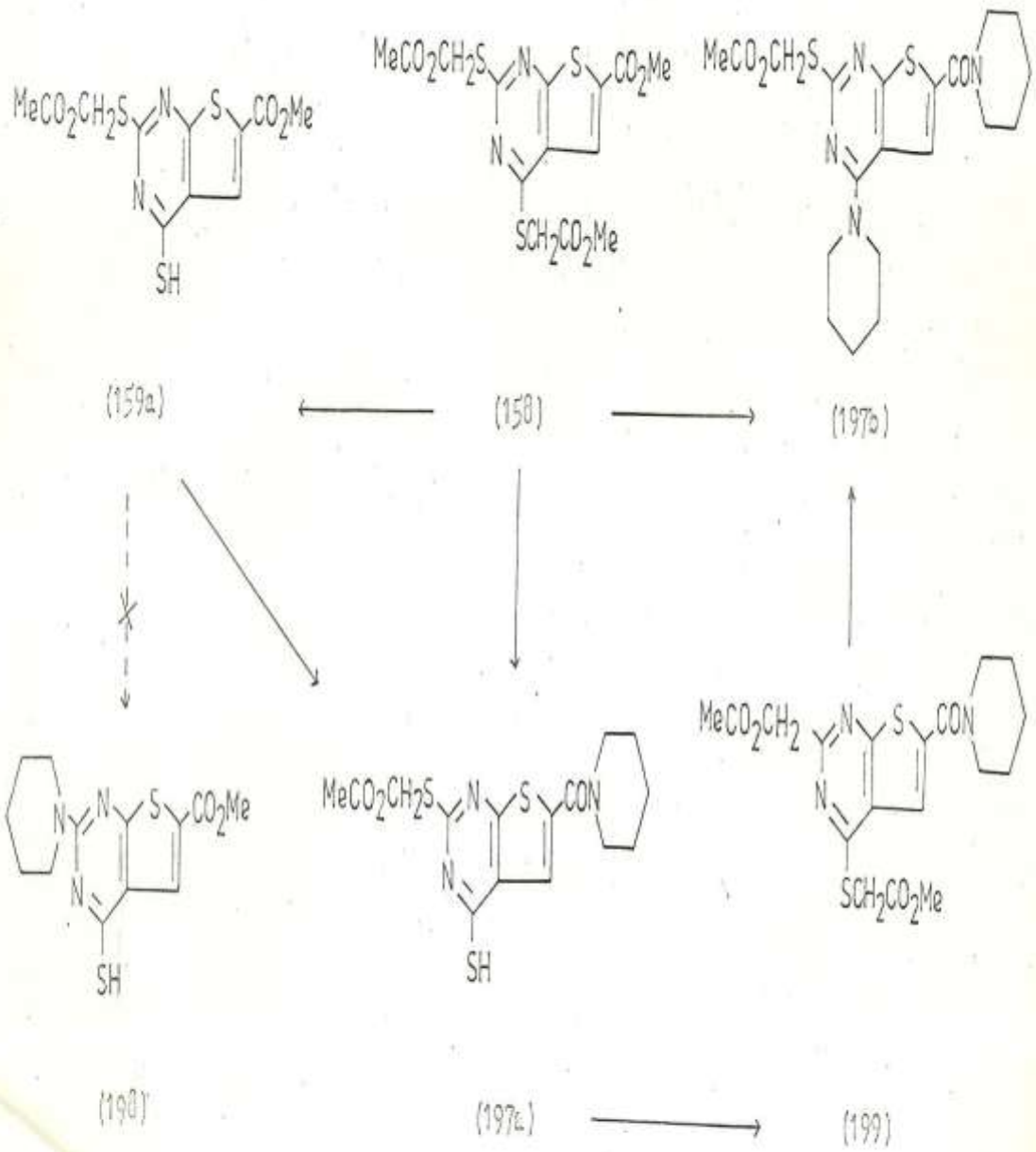

MeS
N
S
CO2Me
N
SMe
MeCO2CH2S
SCH2CO2Me
SH
NaSMe
NaHS
(160a)
(158)
(159b)
piperidine
NaSMe
MeI
(160b)
(159a)
(192) SCH2CO2Me
Scheme 17

2 would be greater than that of the ester group at position 6 but it was still desirable to study the relative activity of positions 2 and 6.

Reaction of the 4-mercaptothienopyrimidine (159b) with neat piperidine gave the piperidine amide (197a) and not the expected 2-piperidino derivative (198). Condensation of (197a) with methyl chloroacetate gave the 2,4-bis methoxycarbonylmethylthio derivative (199) which reacted with piperidine to give the 4-piperidino derivative (197b: Scheme 18) identical with that isolated from reactions of the thienopyrimidine (158) with neat piperidine at 50°. These reaction sequences showed that, at least for reactions with neat piperidine, the order of reactivities of the groups in the thieno-pyrimidine (158) was 4 > 6-ester > 2. Analytical data for the various compounds could also have fitted the reaction sequence (158) to (159c) to (200) but the infrared spectrum of the final product showed a typical



(200)


MeCO2CH2S
CO2Me
SH
SCH2CO2Me
CON
MeCO2CH2
(159a)
(158)
(197a)
(198)
(199)

Scheme 18

C = O stretching signal for an ester group of the SCH_2CO_2Me type ($\sim$1750 cm^{-1}) rather than an ester group directly attached to a thiophen ring ($\sim$1710 cm^{-1}).

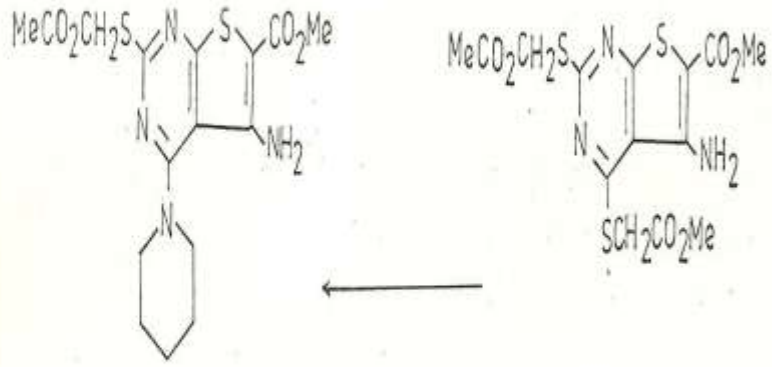
Reactions of the bis(methoxycarbonylmethylthio)-thienopyrimidine (158) with neat morpholine also gave the 4-morpholino compound (159d) and its 6-amide (197c) derivative (Scheme 16). When condensation of (158) with a little more than two equivalents of benzylamine in toluene or hydrazine hydrate in ethanol was carried out at reflux temperature, the 4-(substituted amino)-6-amides (197 d and e; Scheme 16) were isolated. Thus three different amines; morpholine, benzylamine and hydrazine had all reacted preferentially at position 6, rather than position 2, after the leaving group at position 4 was replaced.

It seemed clear that under controlled conditions the desired final product could be prepared with the desired substituents in positions 4, 6 and 2. The three different substituents could be introduced in this order by three successive nucleophilic replacements. However, condensation of the thienopyrimidine (158) with neat pyrrolidine unexpectedly gave the 2,4-dipyrrolidino derivative (160c) after 30 minutes reflux and its 6-amide (161a) (Scheme 16) after 3 hours reflux. Isolation of the 2,4-dipyrrolidino derivative (160c) indicates that in the case of pyrrolidine, the relative reactivities of the groups in the thienopyrimidine (158) was 4>2>6-ester.

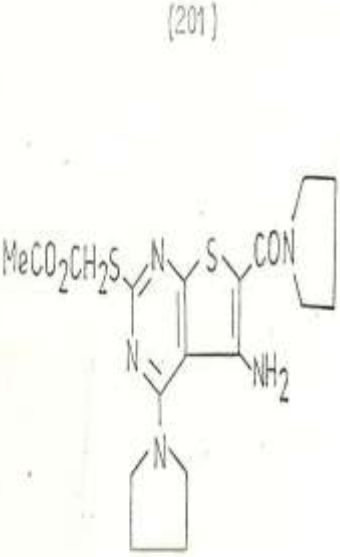
Reaction of the thienopyrimidine (158) with sodium ethoxide was carried out in ethanol under reflux to give the transesterified 2,4-diethoxy derivative (161b), but the 4-methoxy derivative (159c) was isolated when the thienopyrimidine (158) and sodium methoxide in methanol were heated under reflux for 10 minutes.

The pattern of relative reactivities in the thienopyrimidine (158) with nucleophiles was well established in the previous paragraphs. It was decided to compare the relative reactivities of the three active sites, in the 5-amino analogue (165; Scheme 19), towards nucleophiles under similar controlled conditions. For example, reaction of (165) with piperidine at room temperature gave the expected 4-piperidino derivative (201) and with pyrrolidine at 50° gave the 4-pyrrolidino-6-amide (202: Scheme 19). When the condensation of the thienopyrimidine (165) with a methanolic solution of sodium methyl mercaptide was allowed to proceed at room temperature for 12 hours, the expected 2,4-bis-methylthio derivative (203) was isolated. Also, when the reaction of (165) with an ethanolic solution of sodium ethoxide was carried out under reflux for one hour the expected transesterified 2,4-diethoxy derivative (204) (Scheme 19) was isolated.

It can therefore be assumed that the relative reactivities of the three active sites in the 5-amino thienopyrimidine (165) are unaffected by the primary amino group and the order of reactivities of those groups towards amines 4 > 6-ester > 2.



(165)



(201)

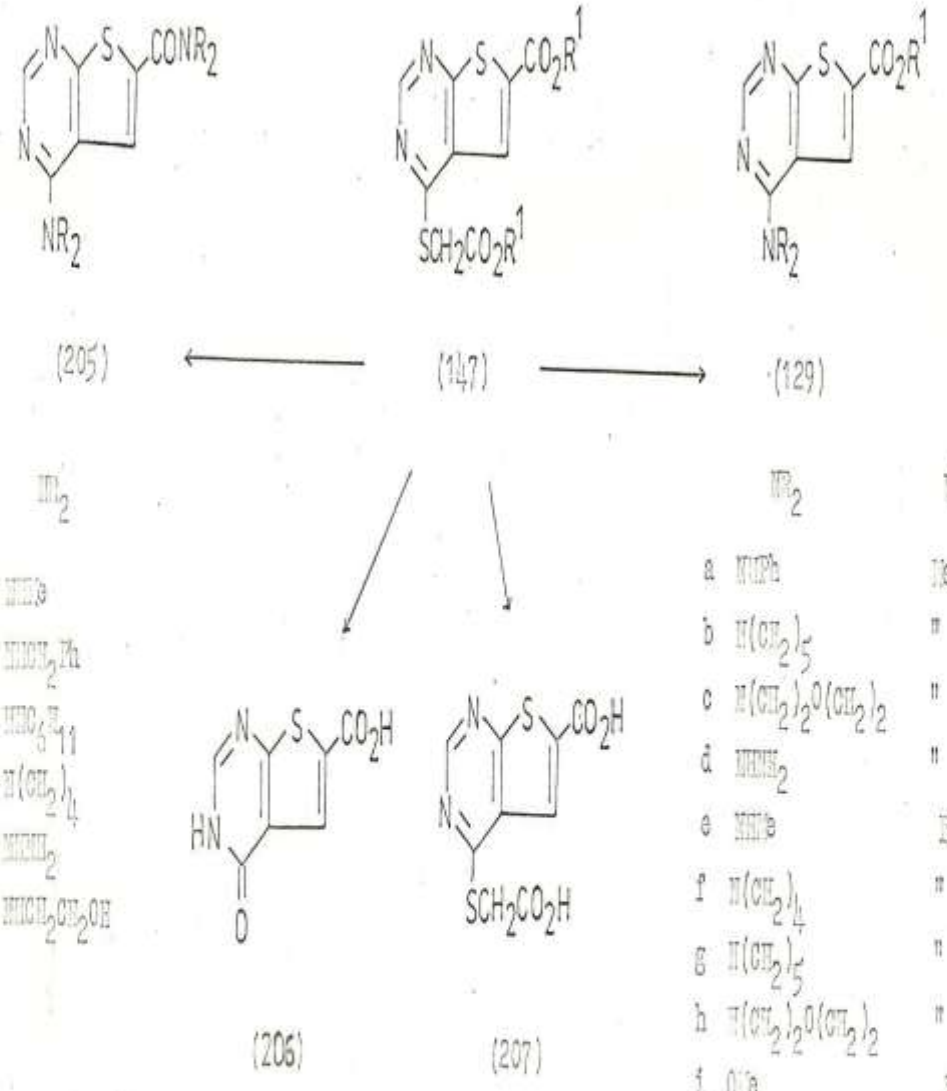
(202) (203) (204)

Schema 19

The behaviour of 2,4-bis-(substituted methylthio)-thienopyrimidines (158 and 165) towards nucleophiles also provided the possibility of predicting the relative reactivities of the groups at position 4 and the 6-ester groups in the 2-unsubstituted thienopyrimidines (147; R^1 = Me or Et) and the 5-amino analogue (153) (Schemes 7 and 8, respectively). The groups at position 4 were more reactive towards nucleophilic substitution reactions than the ester group at position 6. However, it was also expected to find the 6-ester reactive towards nitrogen nucleophiles once the group at position 4 was replaced.

Reactions of the thienopyrimidines (147; R = Me or Et) with neat amines at 50° or with one equivalent of hydrazine hydrate in ethanol at reflux temperature gave the expected 4-substituted derivatives (129 a-h; Scheme 20). However, when the reactions of (147) with neat amines were allowed to proceed at 95°, the expected 4-substituted 6-carboxamides (205 a-f; Scheme 20) were isolated.

Oxygen and sulphur nucleophiles also attacked position 4 in the thienopyrimidine (147; R^1 = Me). For example, treatment with a methanolic solution of sodium methoxide, sodium methyl mercaptide or sodium hydrogen sulphide gave the appropriate 4-substituted derivative (129 i-k) and with an ethanolic solution of sodium ethoxide, the transesterified 4-ethoxy derivative (129 l) was formed (Scheme 20). However, reaction of the thieno-



	NR_2	R^1
a	NHPh	Me
b	$N(CH_2)_5$	"
c	$N(CH_2)_2O(CH_2)_2$	"
d	$NHNH_2$	"
e	NHMe	Et
f	$N(CH_2)_4$	"
g	$N(CH_2)_5$	"
h	$N(CH_2)_2O(CH_2)_2$	"
i	OMe	Me
j	SMe	"
k	SH	"
l	OEt	Et

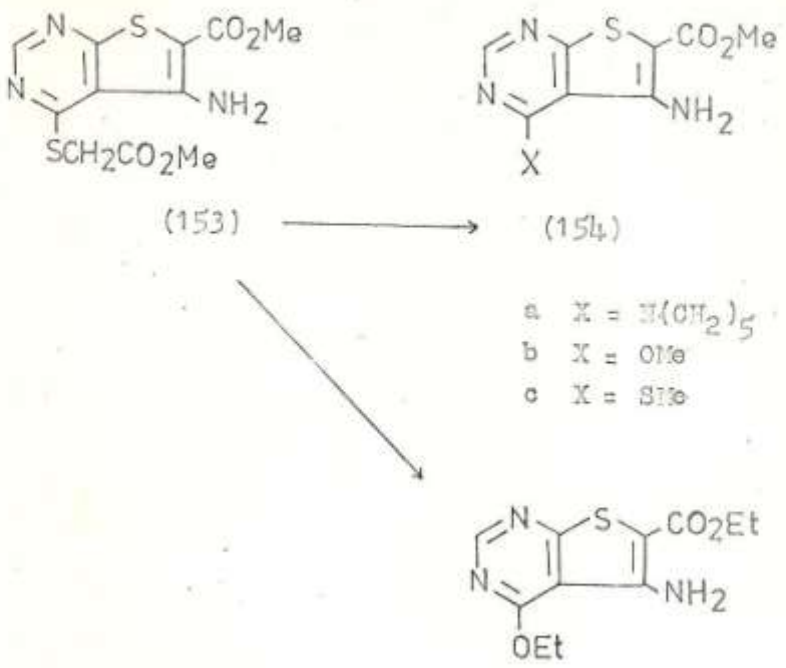
	NR_2
a	NHMe
b	$NHCH_2Ph$
c	NHC_6H_{11}
d	$N(CH_2)_4$
e	$NHNH_2$
f	$NHCH_2CH_2OH$

Scheme 20

pyrimidine (147; R^1 = H) with an aqueous solution of 2N-sodium hydroxide at room temperature gave the 4-hydroxy-6-carboxylic acid derivative (206). When the reagent was dilute ethanolic sodium hydroxide, the ethyl ester (147; R^1 = Et) gave the 4-carboxymethylthio-6-carboxylic acid derivative (207) (Scheme 20). The isolation of such carboxylic acid, (206 and 207) also indicates the ease of hydrolysis of the 6-ester groups as well as replacement or hydrolysis of the 4-alkoxycarbonylmethylthio group.

Reactions of the 5-amino analogue (153) with nucleophiles were expected to give analogous derivatives to those obtained from (147). This was found to be true when the 5-aminothienopyrimidine (147) reacted with neat piperidine or with a methanolic solution of sodium methoxide or sodium methyl mercaptide gave the appropriate 4-substituted derivative (154 a-c). However, with an ethanolic solution of sodium ethoxide, the 4-ethoxy transesterified derivative (208) was isolated (Scheme 21).

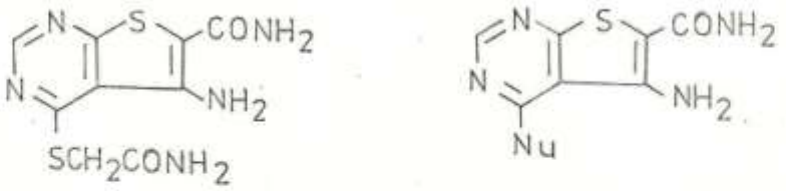
Such reactions with nucleophiles were also tried with the thienopyrimidine (177; X = $CONH_2$) to determine the ease of replacement of the 4-aminocarbonylmethylthio group. For example, condensation of (177c) with neat pyrrolidine, or a methanolic solution of sodium methoxide or sodium hydrogen sulphide, under similar conditions to those used above, gave the appropriate 4-substituted derivative (178 a-c) (Scheme 21).



(153) ⟶ (154)

a X = H(CH$_2$)$_5$
b X = OMe
c X = SMe

(208)



(177f) ⟶ (178)

a Nu = H(CH$_2$)$_4$
b Nu = OMe
c Nu = SH

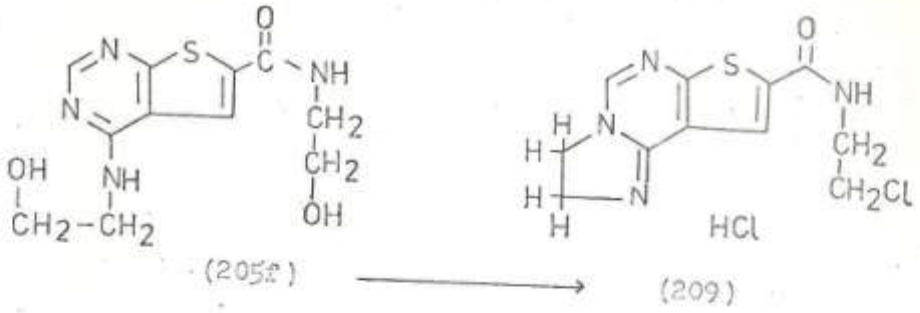
Scheme 21

Although many substituted methylthio groups in the thienopyrimidine system had been readily displaced by nucleophiles phenacylthio groups proved to be exceptional. 4-Phenacylthiothieno[2,3-d]pyrimidines were inert to nucleophiles under conditions where displacement of alkoxycarbonylmethylthio compounds reacted readily. It is possible that the bulky phenacylthio group causes steric hindrance to nucleophilic substitution.

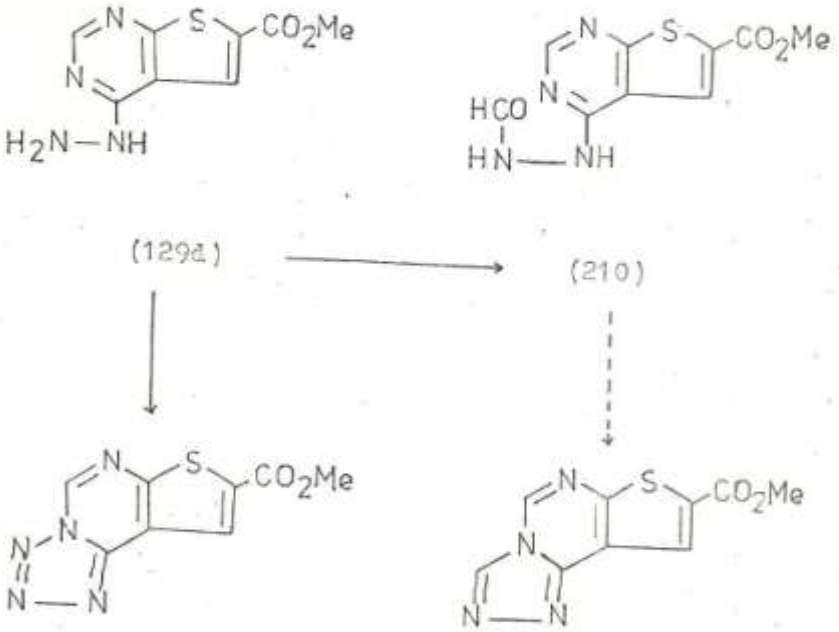
Thienopyrimidines with 4-hydroxyethylamino or hydrazino groups in the pyrimidine ring are potentially suitable for building another ring onto the pyrimidine.

Many examples are cited in the literature whereby a group such as β-hydroxyethylamino in position 2 or 4 of the pyrimidine ring was converted to a chloroethylamino group which then cyclised onto a pyrimidine nitrogen atom to give a hydrochloride salt of an imidazopyrimidine.[215-217] Similarly, hydrazino groups in positions 2 or 4 in the pyrimidine ring would react with formic acid or nitrous acid to give triazolo- or tetrazolopyrimidine respectively.[16,26,34]

A nucleophilic displacement reaction gave a suitable thienopyrimidine (205f; Scheme 22) with β-hydroxyethylamino group at position 4, which was converted to the reduced imidazothienopyrimidine hydrochloride (209) when heated under reflux in thionyl chloride.



(205a) → (209)



(129a) → (210)

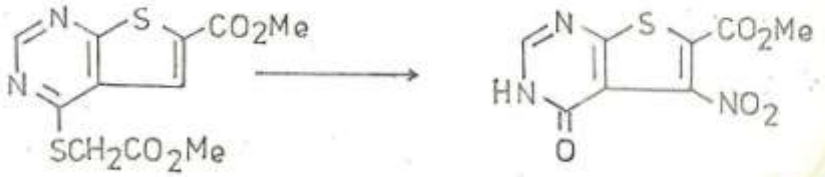
(129a) → (212)

(210) ⇢ (211)

Scheme 22

The 4-hydrazino derivative (129 d) gave the formylated derivative (210) when refluxed in formic acid for 30 minutes. Cyclisation to the triazolo-thienopyrimidine (211) in formic acid was not successful possibly due to the short time of reaction. However, reaction of the hydrazino compound (129 d) with sodium nitrite in glacial acetic acid gave the tetrazolo-thienopyrimidine (212) (Scheme 22). Cyclisation to the tetrazole was indicated by the lack of an azide absorption in the infrared spectrum.

The vacant 5-position in the thienopyrimidine (147; R^1 = Me; Scheme 20) may be considered an active site for electrophilic substitution reactions. Attempts to chlorinate or brominate this position were unsuccessful even under severe conditions but nitration gave the 4-hydroxy-5-nitro compound (213) under several different sets of conditions. Nitration of the thieno-pyrimidine (129 i, Scheme 4) gave the expected 5-nitro derivative (214) without affecting the 4-substituent.



(147) (213)

(129i) (214)

PHYSICAL DATA OF SOME THIENO[2,3-d]PYRIMIDINES

Ultraviolet Spectra

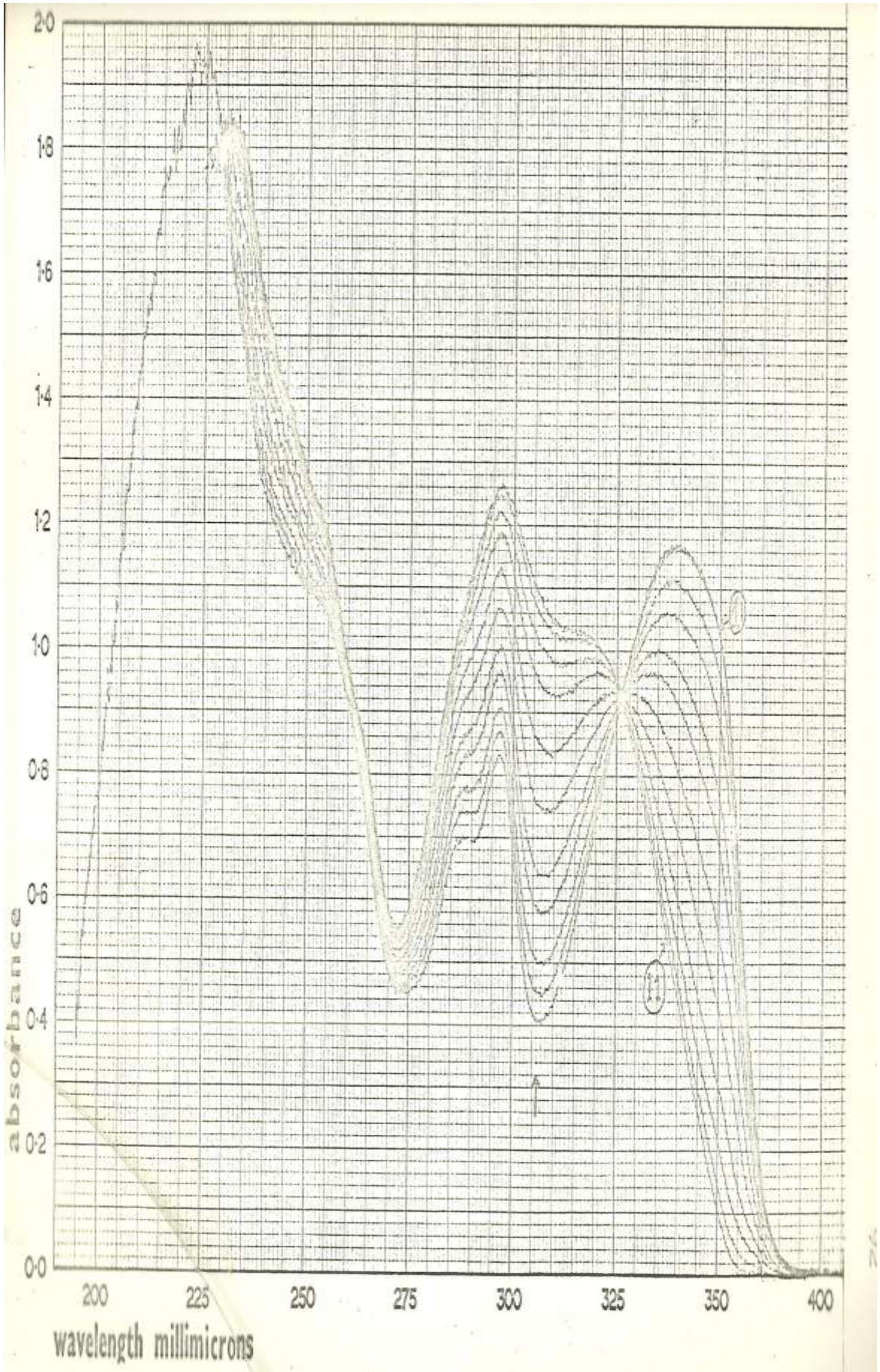
Ionisation constants

The ionisation constants of some representative examples of thieno[2,3-d]pyrimidines were measured by a rapid spectrophotometric method.[220] A typical determination is illustrated in figure (1), which shows the change in ultraviolet spectrum of ethyl 4-pyrrolidino-thieno[2,3-d]pyrimidine-6-carboxylate with changes in pH.

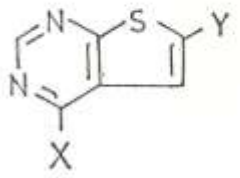
pKa values are given in the table on page 93.

Infrared Spectra

Infrared spectra were particularly useful for elucidating the results of nucleophilic substitution reaction of thienopyrimidines. The carbonyl stretching frequency of an ester group of an $-SCH_2CO_2R$ group was readily distinguished from that of $-CO_2R$ group directly attached to the 6-position of a thienopyrimidine. Furthermore, when SCH_2CO_2R groups were present at both position 2 and 4 of the thienopyrimidine system,


2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
absorbance
200
225
250
275
300
325
350
400
wavelength millimicrons

carbonyl stretching absorbtions for both were visible (see Table 5).

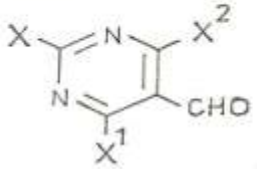


X	Y	pKa value ±	
NH_2	CO_2Et	3.31	0.05
NHMe	CO_2Et	3.23	0.02
$N(CH_2)_4$	CO_2Et	3.62	0.05
$N(CH_2)_5$	CO_2Me	3.34	0.04
NHEt	COPh	3.34	0.04
$N(CH_2)_4$	COPh	3.53	0.05
$N(CH_2)_4$	$CONH_2$	3.73	0.03
$N(CH_2)_4$	CN	3.02	0.05

Nuclear Magnetic Resonance and Mass Spectra

Spectra of some representative examples of pyrimidines and thieno[2,3-d]pyrimidines are shown in Tables 3, 4 and 5.

Physical Data of Some Substituted Pyrimidine-5-carbaldehydes



Compound	Solvent	^{1}H N.M.R.[a] Spectrum[b]	Assignment	Infrared Spectrum[c] (cm^{-1})	λ_{max}^{EtOH} [d]
$X = X^1 = Cl$ $X^2 = NHCH_2Ph$	$CDCl_3$[e]	4.84d, J = 6(2H); 7.40s(5H); 9.80 - 10.20s(br)(1H)[f]; 10.90s.	CH_2; Ph; NH; 5-CHO	1655 (CO)	282
$X = X^1 = Cl$ $X^2 = N(CH_2Ph)_2$	$CDCl_3$	4.75d, J = 7(4H); 7.00-7.22m (10H); 10.20s	$2CH_2$; 2Ph; 5-CHO	1680 (CO)	372
$X = X^1 = Cl$ $X^2 = N(CH_2)_5$	$CDCl_3$[g]	1.70s(br)(6H), 3.60s(br)(2H), 3.90s(br)(2H); 10.20s	$N(CH_2)_5$; 5-CHO	1675 (CO)	260

continued

Table 3 (continued)

I	II	III	IV	V	VI
X = X^1 = Cl X^2 = $N(CH_2)_6$	$CDCl_3$[e]	1.50-2.00m(8H), 3.50t J = 6(4H), 10.50s	$N(CH_2)_6$; 5-CHO	1675 CO)	274
X = H X^1 = SH (or thione) X^2 = $NHCH_2Ph$	d_6D.M.S.O.[h]	3.00-3.50s(br)(1H)[f]; 4.75d J = 6(2H); 7.25s; 8.05s; 10.15s(br)(1H); 10.45s	4-NH; CH_2; Ph; 2-H; 1-NH; 5-CHO	3270 (N-H) broad; 1670 (CO)	245
X = H X^1 = SH (or thione) X^2 = $NHCH_3$	$CDCl_3$[e,i]	1.28t J = 7(3H); 3.45-3.85m (2H); 4.45-4.65s(br)[f]; 7.95s; 9.60-9.90s(br)[f]; 10.50s	CH_3; CH_2; 4-NH; 2-H; 1-NH; 5-CHO	3250 (N-H) broad; 3150 (N-H); 1650 (CO)	183
X = H X^1 = SH(or thione) X^2 = NMe_2	d_6D.M.S.O.	3.10s(6H); 7.95d J = 4(1H); 10.40s; 13.65-14.00s(br)[f]	$2CH_3$; 2-H; 5-CHO; 1-NH	3150 (N-H) broad; 1670 (CO)	183

continued

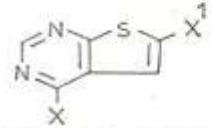
Table 3 (continued)

I	II	III	IV	V	VI
X = H X^1 = X^2 = SCH_2CO_2Me	$CDCl_3$ [g,j]	3.75s(6H); 4.05s(4H); 8.70s (1H); 10.62s(1H)	$2CH_3$; $2CH_2$; 2-H; 5-CHO	1745 (CO) esters (broad) 1690 (CO) formyl	316
X = SMe X^1 = X^2 = SCH_2CO_2Me	$CDCl_3$	2.53s(3H); 3.73s(6H); 3.95s (4H); 10.55s(1H)	SCH_3; $2CH_3$; $2CH_2$; 5-CHO	1750 (CO) esters 1730 (CO) 1680 (CO) formyl	362

[a]Unless otherwise indicated, all spectra were measured on a Varian EM360 spectrometer at normal probe temperature using tetramethylsilane as internal standard. [b]Signals are given in the form:- chemical shift (δ) multiplicity, coupling constant (Hz) and number of protons (br = broad, s = singlet, d = doublet, t = triplet, m = multiplet). [c]Measured on a Perkin-Elmer 257 spectrometer. [d]Measured on an AEI MS 12 spectrometer. [e]Measured on a Varian A 60A spectrometer. [f]Signal disappears on deuteration. [g]Measured on a Perkin-Elmer R32 spectrometer. [h]D.M.S.O. = $(CD_3)_2SO$. [i]With few drops of $(CD_3)_2SO$.

TABLE 4

Physical Data of Some 4,6-disubstituted Thieno[2,3-d]pyrimidines



Compound	Solvent	^{1}H N.M.R.[a] Spectrum[b]	Assignment	Infrared Spectrum[c] (cm^{-1})	M.P.[d]
X = SCH_2CO_2Me X^1 = CO_2Me	$CDCl_3$[1]	3.75s(3H); 3.98s(3H); 4.15s (2H); 7.95s; 8.75s	6-OCH_3; 4-OCH_3; SCH_2; 5-H; 2-H	1745 (CO) broad esters	298
X = NHMe X^1 = CO_2Me	$CDCl_3$[e,i]	3.00s(3H); 3.08d J = 6(3H); 7.80-8.00s(br)[f]; 8.35s; 8.45s	OCH_3; NCH_3; NH; 5-H; 2-H	3180 (NH) broad; 1735 (CO) ester	-
X = NMe_2 X^1 = CO_2Me	d_6D.M.S.O.[h]	3.20s(3H), 3.42s(3H); 3.85s(3H); 7.96s(1H); 8.10s(1H)	$N(CH_3)_2$; OCH_3; 5-H; 2-H	1725 (CO) ester	-

continued

Table 4 (continued)

I	II	III	IV	V	VI
X = NEtPh X^1 = CO_2Me	$CDCl_3$	1.30t J = 7(3H); 4.03q J = 7(2H); 3.70s(3H); 6.00s(1H); 7.10-7.51m(5H); 8.50s	CH_3(Et); CH_2(Et); OCH_3; 5-H; Ph; 2-H	1715 (CO) ester	313
X = OMe X^1 = CO_2Me	$CDCl_3$	3.95s; 4.15s; 8.05s; 8.70s	4-OCH_3; 6-OCH_3; 5-H; 2-H	1725 (CO) ester	224
X = OCH_2CO_2Et X^1 = CO_2Et	$CDCl_3$	1.30q J = 7(6H); 4.25q J = 7 (4H); 4.05s(2H); 8.00s; 8.79s	2CH_3; 2CH_2 (ethyl); OCH_2; 5-H; 2-H	1725 (CO) both esters	325
X = NH_2 X^1 = CO_2Et	$CDCl_3$	1.45t J = 7(3H); 4.35q J = 7 (2H); 7.88s(1H); 8.35s(1H); 4.08s(2H)	CH_3; CH_2; 5-H; 2-H; NH_2	3420 (NH) 3340 (NH) 1700 (CO)	-

continued

Table 4 (continued)

I	II	III	IV	V	VI
X = NHNa X^1 = CO_2Et	$CDCl_2$[e]	1.45t J = 7(3H); 4.45q J = 7(2H); 3.14d J = 4(3H); 7.90-8.20s(br)[f]; 8.50s; 8.62s	CH_3; CH_2; NCH_3; NH; 5-H; 2-H	3280 (NH); 1725 (CO)	237
X = NHEt X^1 = CO_2Et	$CDCl_3$[e,i]	1.37q J = 7(6H); 3.76q J = 7(2H); 4.44q J = 7(2H); 7.30-7.60s(br)[f]; 8.40s; 8.70s	2CH; CH_2(N-ethyl); CH_2 (o-ethyl); NH; 5-H; 2-H	3250 (NH); 1720 (CO)	251
X = $N(CH_2)_4$ X^1 = CO_2Et	$CDCl_3$	1.38t J = 7(3H); 1.90-2.20m (4H), 3.50-3.90m(4H); 4.33q J = 7(2H); 7.87s; 8.25s	CH_3; $N(CH_2)_4$; OCH_2; 5-H; 2-H	1690 (CO)	277
X = $N(CH_2)_5$ X^1 = CO_2Et	CCl_4	1.38t J = 7(3H); 4.40q J = 7(2H); 1.60-1.80m(6H), 3.70-4.00m(4H); 7.85s; 8.25s	CH_3; CH_2; $N(CH_2)_5$; 5-H; 2-H	1715 (CO)	291
X = $N(CH_2)_2O(CH_2)_2$ X = CO_2Et	CCl_4-$CDCl_3$	1.40t J = 7(3H); 4.35q J = 7(2H); 3.85-3.90m(8H); 7.95s; 8.40s	CH_3; CH_2; $N(CH_2)_2O(CH_2)_2$; 5-H; 2-H	1695 (CO)	293

continued

Table 4 (continued)

I	II	III	IV	V	VI
X = NHEt X^1 = COPh	$CDCl_3$	1.28t J = 7(3H); 3.45-3.65m(2H); 3.10s(1H)[f]; 7.45-7.95m(5H); 8.28s; 8.40s	CH_3; CH_2; NH; Ph; 5-H; 2-H	1680 (CO)	283
X = NMe_2 X^1 = COPh	$CDCl_3$[g]	3.35s(6H); 7.40-7.60m(3H), 7.20-7.80m(2H); 7.95s; 8.40s	$N(CH_3)_2$; Ph; 5-H; 2-H	1685 (CO)	283
X = $N(CH_2)_4$ X^1 = COPh	$CDCl_3$	1.95-2.18m(4H); 3.65-3.85m(4H); 7.48-7.75m(5H); 7.93s; 8.42s	$N(CH_2)_4$; Ph; 5-H; 2-H	1680 (CO)	309
X = $N(CH_2)_5$ X^1 = COPh	d_6D.M.S.O.[h]	1.50-1.90m(6H), 3.70-3.95m(4H); 7.55-7.85m(5H); 8.10s; 8.30s	$N(CH_2)_5$; Ph; 5-H; 2-H	1685 (CO)	337

continued

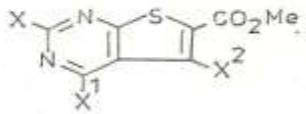
Table 4 (continued)

I	II	III	IV	V	VI
X = N=CMe$_2$ X^1 = CONH	d_6D.M.S.O.[b]	2.75s(6H); 7.21-7.50m(3H), 7.90 8.10m(2H); 8.32s; 8.90s	$2CH_3$; Ph, 5-H; 2-H	1685 (CO)	295
X = N$(CH_2)_4$ X^1 = COC_6H_4Br(p)	d_6D.M.S.O.[b]	1.90-2.20m(4H), 3.63-3.85m(4H); 7.65s(4H); 7.90s; 8.40s	N$(CH_2)_4$; C_6H_4; 5-H; 2-H	1675 (CO)	387-388

a - i as in Table 3

TABLE 5

Physical Data of Some Methyl polysubstituted thieno[2,3-d]pyrimidine-6-carboxylates



Compound	Solvent	^{1}H N.M.R.[a] Spectrum[b]	Assignment	Infrared Spectrum[c] (cm^{-1})	M.p.[d]
X = H, X^1 = OMe, X^2 = NH_2	$CDCl_3$[g]	3.90s(3H); 4.20s(3H); 6.40-6.60s(br)[f]; 8.60s	OCH_3; CH_3 (ester); NH_2; 2-H	3440 (NH) 3340 (NH) 1685 (CO)	-
X = H, X^1 = OH, X^2 = NO_2	d_6D.M.S.O.[h]	3.85s(3H); 5.84s(1H)[f]; 8.25s(1H)	CH_3; NH; 2-H	3150 (NH); 1765 (CO)	255
X = X^1 = SCH_2CO_2Me X^2 = H	$CDCl_3$	3.78s(6H); 3.97d J 4(4H); 4.10s(3H); 7.85s(1H)	$2OCH_3$; $2CH_2$; 6-CH_3; 5-H	1770 (CO)2-ester, 1750 (CO)4-ester 1730 (CO)6-ester	-

continued

Table 5 (continued)

I	II	III	IV	V	VI
X = $SCH_2CO_2^{\ominus}$ X^1 = $S^{\oplus}$ X = H	$CDCl_3$	2.60s(3H); 3.70s(3H); 3.90s (2H); 4.00s(3H); 7.85s(1H)	SCH_3; 2-OCH_3; CH_2; 6-OCH_3; 5-H	1755 (CO)2-ester 1710 (CO)6-ester	-
X = $S^{\oplus}$ X^1 = $SCH_2CO_2^{\ominus}$ X^2 = H	$CDCl_3$	2.53s(3H); 3.74s(3H); 3.80s(3H); 4.05s(2H); 8.10s(1H)	SCH_3; 4-OCH_3; 6-OCH_3; CH_2; 5-H	1740-1720 broad (CO) 4- and 6-esters	-
X = $S^{\oplus}$ X^1 = $N(CH_2)_5$ X^2 = H	$CDCl_3$	1.70-1.80m(6H), 3.82-3.92m (4H); 2.50s; 3.80s; 7.98s	$N(CH_2)_5$; SCH_3; OCH_3; 5-H	1710 (CO)	-
X = $SCH_2CO_2^{\ominus}$ X^1 = $N(CH_2)_5$ X^2 = H	$CDCl_3$	1.70-1.82m(6H), 4.48s(4H); 4.29s(3H); 4.32s(3H); 8.58s (1H)	$N(CH_2)_5$, 2-OCH_3; 6-OCH_3; 5-H	1740 (CO)2-ester 1710 (CO)6-ester	-

continued

Table 5 (continued)

I	II	III	IV	V	VI
$X = X^1 = SiMe$, $X^2 = H$	$CDCl_3$	2.70s(3H), 2.75s(3H); 3.95s(3H); 7.90s(1H)	2 OCH_3;– OCH_3; 5-H	1745 (CO)2-ester 1705 (CO)6-ester	325
$X = CH_2CO_2Me$ $X^1 = CMe$ $X^2 = NH_2$	$CDCl_3$	3.72s(3H); 3.82s(3H); 3.92s(2H); 4.09s(3H); 6.30-6.40s(br)[f]	4-OCH_3; 2-OCH_3; CH_2 6-OCH_3; NH_2	3530 (NH) 3415 (NH) 1740 (CO)2-ester 1685 (CO)6-ester	340
$X = X^1 = SiMe$, $X^2 = NH_2$	$CDCl_3$	2.56s(3H); 2.70s(3H); 3.88s (3H); 6.42-6.60s(br)[f]	4-OCH_3; 2-OCH_3; 6-OCH_3; NH_2	3440 (NH) 3325 (NH) 1685 (CO)	301

a - i as in Table 3

EXPERIMENTAL

CHAPTER XI

SYNTHESES AND REACTIONS OF 4-(SUBSTITUTED AMINO)-6-CHLOROPYRIMIDINE-5-CARBALDEHYDES

Condensation of 4,6-dichloropyrimidine-5-carbaldehyde with amines[194,197].- The 4-(substituted amino)-6-chloropyrimidine-5-carbaldehydes employed were synthesised by the following two general methods.

a) The appropriate amine (0.1 mole) and triethylamine (0.1 mole) were added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde,[193] (0.1 mole) in dry chloroform at 0°. Stirring was continued at room temperature for a further 3 hours when reaction mixture was washed with water and dried with anhydrous magnesium sulphate. The chloroform was distilled under reduced pressure leaving an oil which solidified on cooling.

b) The appropriate amine (0.2 mole) was neutralised to pH 8 by addition of 50% glacial acetic acid and added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde (0.1 mole) in dioxan at 10-15°. Stirring was continued at room temperature for a further 3 hours when the reaction mixture was poured into cold water and the precipitated product filtered off, washed and crystallised.

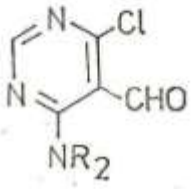
Melting points, yields and crystallisation solvents are recorded in Table 6.

4-Amino-6-chloropyrimidine-5-carbaldehyde[194].- Anhydrous ammonia was bubbled through a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde (0.1 mole) in dry benzene (50 ml) at 0° for 3 hours. The solid precipitated was filtered, washed with water and dried.

TABLE 6

4-(Substituted amino)-6-chloropyrimidine-5-carbaldehydes

(123)



NR_2	Yield %	M.P.	Crystallisation solvent	Method
NHMe	75	158°	propan-2-ol	a
NHEt	70	77	"	a
$NHCH_2CH{:}CH_2$	75	78	"	a
$NHCH_2Ph$	85	77	"	a
$N(CH_2)_4$	80	116	"	a
$N(CH_2)_5$	80,85	79	"	a,b
$N(CH_2)_6$	80	110	"	a
$N(CH_2)_2O(CH_2)_2$	95	93	"	a
NMe_2	80	139	"	a
NEtPh	75,80	117	"	a,b
NH_2	90	170(d)	-	-

2,4,6-Trichloropyrimidine-5-carbaldehyde[199].- N,N-Dimethylformamide (42 ml) was added dropwise over a period of 30 minutes to stirred phosphoryl chloride (130 ml) at 0°. The solution was kept for a further 30 minutes before babituric acid (30 g) was added. The reaction mixture was gently heated at 90° for 18 hours and the resulting deep brown solution was cooled to room temperature and poured onto ice (800 g). After 10 minutes the temperature was allowed to rise to about 50° when a solid began to precipitate. The temperature was lowered by cooling in a water bath and stirring was continued for a further 10 minutes. The yellow solid was filtered off, washed with water and crystallised from ethyl acetate to yield 2,4,6-trichloropyrimidine-5-carbaldehyde (30 g), m.p. 132°, identical with that from a (different) published work-up procedure.[199]

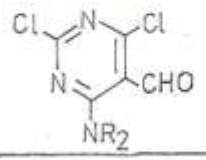
Condensation of 2,4,6-trichloropyrimidine-5-carbaldehyde with amines.- 4-(Substituted amino)-2,6-dichloropyrimidine-5-carbaldehydes were prepared by the methods (a) and (b) described for the condensation of 4,6-dichloropyrimidine-5-carbaldehyde with amines. Melting points, yields and elemental analyses of the products are recorded in Table 7.

4-Amino-2,6-dichloropyrimidine-5-carbaldehyde, m.p. 200° (decomp) was prepared in 90% yield from 2,4,6-trichloropyrimidine-5-carbaldehyde by a similar method to that described for the 4-amino-6-chloropyrimidine-5-carbaldehyde. The product was identical with that from a (different) published method.[193]

TABLE 7

4-(Substituted amino)-2,6-dichloropyrimidine-5-carbaldehydes

(132)



NR_2	Yield %	M.P.	Crystallisation solvent	Method	Found (%) C	H	N	Required (%) C	H	N
NH_2	90	d>200°	-	-	31.3	1.6	22.3	31.3	1.6	21.9
$NHCH_2Ph$	74	106	propan-2-ol	a	51.0	3.2	15.0	51.0	3.2	14.9
$N(CH_2Ph)_2$	75	88	"	b	61.0	4.1	11.4	61.3	4.0	11.3
$N(CH_2)_4$	75	82	"	b	44.3	3.7	17.7	43.9	3.7	17.1
$N(CH_2)_5$	75	102	"	b	46.0	4.6	16.2	46.1	4.2	16.1
$N(CH_2)_6$	50	120	"	b	48.5	4.8	15.7	48.1	4.7	15.3
NHC_6H_{11}	55	125	"	a	48.2	4.8	15.7	48.2	4.7	15.3

Condensation of 4-(substituted amino)-6-chloropyrimidine-5-carbaldehydes with methyl or ethyl thioglycolate.- 4-(Substituted amino)thieno[2,3-d]-pyrimidines were prepared from the corresponding 4-(substituted amino)-6-chloropyrimidine-5-carbaldehyde by the following three general methods.

c) Ethyl thioglycolate (0.01 mole) was added dropwise to a stirred solution of the appropriate 4-(substituted amino)-6-chloropyrimidine-5-carbaldehyde (0.01 mole) and triethylamine (0.01 mole) in N,N-dimethylformamide (25 ml) at room temperature. After a few minutes the solid which appeared was redissolved by addition of 2N-potassium hydroxide (2 ml). Stirring was continued at room temperature for a further 5 hours when the reaction mixture was added to cold water. The product was filtered off, washed with water and crystallised from a suitable solvent.

d) The appropriate 4-(substituted amino)-6-chloro-pyrimidine-5-carbaldehyde (0.01 mole), ethyl thioglycolate (0.01 mole) and anhydrous sodium carbonate (2.0 g) were heated under reflux in ethanol (25 ml) for 2 hours. The solvent was evaporated under reduced pressure to near dryness and the residue stirred with cold water (25 ml) for a few minutes. The product was filtered off, washed with water and crystallised from a suitable solvent.

e) The appropriate 4-(substituted amino)-6-chloropyrimidine-5-carbaldehyde (0.01 mole), methyl thioglycolate (0.01 mole) and triethylamine (0.01 mole) were heated under reflux in methanol (50 ml) for 2 hours. The work-up procedure was the same as that described in method (d).

The melting points, yields, crystallisation solvents and elemental analyses of the products are recorded in Table 8.

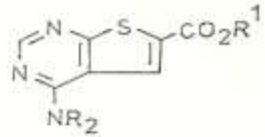
4-Amino-6-ethoxycarbonylmethylthiopyrimidine-5-carbaldehyde.- Condensation of 4-amino-6-chloropyrimidine-5-carbaldehyde (3.1 g) with ethyl thioglycolate (2.4 g) and triethylamine (2.2 g) in N,N-dimethylformamide (25 ml) as described in method (c) gave a mixture (4.1 g) of the title compound and ethyl 4-aminothieno[2,3-d]-pyrimidine-6-carboxylate (Table 8). The mixture was separated by boiling it with petroleum ether (b.p. 100-120°) (50 ml) and filtering off the insoluble material while hot. The filtrate was cooled to give the title compound, m.p. 142°. (Found: C, 44.4; H, 4.5; N, 17.7. $C_9H_9N_3O_2$ requires C, 44.8; H, 4.6; N, 17.4%).

The insoluble material from above was digested with a mixture of toluene and ethanol (50/50) (50 ml) to remove any remaining uncyclised material and the insoluble fraction was filtered off from the hot solvent mixture and crystallised from ethanol to yield the thienopyrimidine, m.p. 260° (decomp) (see Table 8).

TABLE 8

Alkyl 4-(substituted amino)thieno[2,3-d]pyrimidine-6-carboxylates

(129)



NR_2	R^1	Yield %	M.P.	Crystn. solvent	Method	Found (%) C	H	N	Required (%) C	H	N
NHMe	Et	75	215°	Pet. ether (b.p. 100-120)	c	50.1	4.5	17.7	50.6	4.6	17.7
NHEt	Et	85	222	"	c	52.3	5.3	16.8	52.6	5.2	16.7
$NHCH_2CH{:}CH_2$	Et	90	180	"	c	54.2	4.9	15.9	54.8	4.9	15.9
$NHCH_2Ph$	Et	70	145	"	c	61.3	4.8	13.4	61.3	4.8	13.6
$N(CH_2)_4$	Et	70,75	160	"	c,d	56.1	5.5	15.1	56.3	5.4	15.1
NH_2	Et	40	260(d)	EtOH	c	48.4	4.3	18.7	48.4	4.0	18.8
NHMe	Me	80	240	MeOH	e	48.1	4.0	19.1	48.4	4.0	18.8

continued

Table 8 (continued)

I	II	III	IV	V	VI	VII			VIII		
$N(CH_2)_2O(CH_2)_2$	Me	70	150	Pet. ether (b.p. 100-120)	e	50.8	4.7	14.4	51.6	4.7	15.0
NMe_2	Me	80	206	"	e	50.3	4.6	18.0	50.6	4.6	17.7
NEtPh	Me	90	179	"	e	61.5	4.9	13.4	61.3	4.8	13.4
NH_2	Me	30	250	DMF	e	45.5	3.4	20.0	45.9	3.3	20.0
$N(CH_2)_4$	Me	90	195	Pet. ether (b.p. 100-120)	e	54.7	5.0	16.0	54.7	4.9	16.0

Condensation of 4-(substituted amino)-2,6-dichloropyrimidine-5-carbaldehydes with methyl or ethyl thioglycolate.- Alkyl 2-alkoxycarbonylmethylthio-4-(substituted amino)thieno[2,3-d]pyrimidine-6-carboxylates were prepared by the following general method.

f) The appropriate 4-(substituted amino)-2,6-dichloropyrimidine-5-carbaldehyde (0.01 mole), alkyl thioglycolate (0.02 mole) and triethylamine (0.02 mole) were heated under reflux in toluene (25 ml) for 6 hours. The reaction mixture was filtered while hot and the filtrate was reduced in volume by distillation and cooled to yield the product in crystalline form (see Table 9).

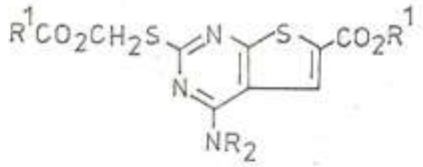
4-Amino-2,6-bis-(ethoxycarbonylmethylthio)pyrimidine-5-carbaldehyde.- 4-Amino-2,6-dichloropyrimidine-5-carbaldehyde (1.9 g, 0.01 mole), ethyl thioglycolate (1.2 g, 0.02 mole) and triethylamine (1.1 g, 0.02 mole) in N,N-dimethylformamide (25 ml) were treated as described in method (c). The product was crystallised from petroleum ether (b.p. 100-120°) to yield the title compound (1.5 g), m.p. 101°. (Found: C, 44.0; H, 4.8; N, 11.6. $C_{13}H_{17}N_3O_5S_2$ requires C, 43.5; H, 4.7; N, 11.7%).

2-Chloro-4-ethoxycarbonylmethylthio-6-pyrrolidinopyrimidine-5-carbaldehyde.- 2,4-Dichloro-6-pyrrolidinopyrimidine-5-carbaldehyde (1.2 g), ethyl thioglycolate (0.6 g) and triethylamine (0.6 g) in N,N-dimethylformamide (25 ml) were treated as in method (c). The product was crystallised from methanol to give the title compound (1.1 g), m.p. 135°. (Found: C, 47.7; H, 4.9; N, 13.0.

TABLE 9

Alkyl 2-alkoxycarbonylmethylthio-4-(substituted amino)thieno[2,3-d]pyrimidine-6-carboxylates

(136)



NR_2	R^1	Yield %	M.P.	Crystn. solvent	Method	Found (%) C	H	N	Required (%) C	H	N
$NHCH_2Ph$	Me	80	181°	Toluene	f	53.4	4.3	10.4	53.6	4.7	10.4
$N(CH_2Ph)_2$	Me	80	161	"	f	60.4	4.8	8.4	60.8	4.7	8.5
$NHCH_2Ph$	Et	85	165	IPA	f	55.4	4.9	9.7	55.7	4.9	9.7

$C_{13}H_{16}N_3ClO_3S$ requires C, 47.3; H, 4.9; N, 12.7%).

Ethyl 2-chloro-4-pyrrolidinothieno[2,3-d]pyrimidine-6-carboxylate.- The uncyclised derivatives obtained above (0.5 g) was heated under reflux in methanol (5 ml) and triethylamine (0.5 g) for 30 minutes. The reaction mixture was cooled to give the title compound in crystalline form (0.4 g), m.p. 180°. (Found: C, 50.0; H, 4.6; N, 13.2. $C_{13}H_{14}N_3ClO_2S$ requires C, 50.0; H, 4.5; N, 13.5%).

Ethyl 2-chloro-4-dibenzylaminothieno[2,3-d]-pyrimidine-6-carboxylate.- 4-Dibenzylamino-2,6-dichloropyrimidine-5-carbaldehyde (1.6 g), ethyl thioglycolate (0.6 g) and triethylamine (0.6 g) in N,N-dimethylformamide (25 ml) were treated as in method (c), but the reaction time was extended to 18 hours. The product was crystallised from petroleum ether (b.p. 100-120°) to yield the title compound (1.8 g), m.p. 150°. (Found: C, 62.4; H, 4.7; N, 9.5. $C_{23}H_{20}N_3ClO_2S$ requires C, 63.0; H, 4.6; N, 9.6%).

CHAPTER XII

SYNTHESES AND REACTIONS OF 4-(SUBSTITUTED AMINO)-5-FORMYLPYRIMIDINE-6(1H)THIONES

4-(Substituted amino)-5-formylpyrimidine-6(1H)thiones.- These were prepared by the following two general methods.

a) The appropriate 4-(substituted amino)-6-chloropyrimidine-5-carbaldehyde (0.01 mole) and thiourea (0.02 mole) were heated under reflux in 80% aqueous ethanol (100 ml) for 3 hours during which solution was obtained followed by precipitation of a yellow solid. The reaction mixture was left to stand at room temperature overnight. The solid was filtered off, washed with water, followed by ethanol, and dried. The mother liquor gave more solid on further standing.

The product was purified by dissolving in 2N-sodium hydroxide (10 ml) and the clear solution was acidified with 2N-hydrochloric acid to give the free thione which was filtered off, washed with water and dried. The product was then crystallised if possible.

b) A methanolic solution of sodium hydrogen sulphide (10 ml) (prepared by passing hydrogen sulphide through a cooled and stirred solution of 2N-sodium methoxide in methanol until the pH was 8) was added dropwise to a stirred solution of a 4-(substituted amino)-6-chloropyrimidine-5-carbaldehyde (0.01 mole) in methanol (10 ml). Reaction was exothermic and

the mixture was stirred for 30 minutes. The solvent was evaporated to near dryness and the residue dissolved in water (10 ml) and the clear solution was acidified with 2N-hydrochloric acid to give the free thione which was filtered off, washed with water, followed by methanol, and dried. The product was crystallised if possible.

Melting points, yields, purification procedures and elemental analyses of products are recorded in Table 10.

Reactions of 4-(substituted amino)-5-formylpyrimidine-6(1H)thiones with halogeno compounds.- 4-(Substituted amino)thieno[2,3-d]pyrimidines were prepared by the following three general methods.

c) The appropriate 4-(substituted amino)-5-formyl-pyrimidine-6(1H)thione (0.01 mole), the appropriate halide (0.01 mole) and anhydrous sodium carbonate (2.0 g) in ethanol (20 ml) were stirred for 18 hours at room temperature. The solid was filtered off and stirred with water (25 ml) for 5 minutes. The thienopyrimidine was filtered off, washed with water, followed by ethanol, dried and crystallised from ethanol.

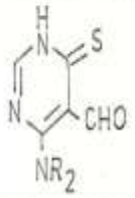
d) As described in method (c) except that the reaction solvent was evaporated under reduced pressure to near dryness and the residue treated with cold water. The thienopyrimidine was filtered off and crystallised from ethanol.

e) As described in method (c), except that the reaction mixture was heated under reflux for 15 minutes.

TABLE 10

4-(Substituted amino)-5-formylpyrimidine-6(1H)thiones

(142)



NR_2	Yield (%)	M.P.	Crystn. Solvent *	Prepn. Method	Found (%) C	H	N	Required (%) C	H	N
$N(CH_2)_4$	50 , 90	200°	MeOH	a,b	51.5	5.3	20.0	51.7	5.3	20.0
$NHCH_2Ph$	50	200 (d)	H_2O/EtOH	a	58.4	4.5	17.0	58.8	4.5	17.1
NH Me	60	240 (d)		a	42.8	4.3	25.0	42.6	4.1	24.9
NH Et	40	200 (d)		a	46.3	5.0	22.5	45.9	4.9	22.9
NMe_2	60	230		a	45.5	5.0	22.6	45.9	4.9	22.9
NH_2	50 , 80	240 (d)	H_2O/EtOH	a,b	38.0	3.0	24.0	38.7	3.2	27.0
$N(CH_2)_5$	50 , 90	200 (d)		a,b	53.8	6.2	18.0	53.8	5.8	18.8

* Where no solvent is shown the product was pure after precipitation from alkali

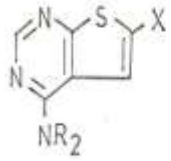
Melting points, yields, halides used, and elemental analyses of products are recorded in Table 11.

4-Amino-5-ethoxycarbonylmethylthiopyrimidine-5-carbaldehyde.- 4-Amino-5-formylpyrimidine-6(1H)thione (0.5 g), ethanol (10 ml), ethyl bromoacetate (1 ml) and triethylamine (1 ml) were heated under reflux for 1 hour. The mixture was evaporated to dryness and the residue was treated with water. The solid was filtered off, washed with water and crystallised from petroleum ether (b.p. 100-120°) to give the product, m.p. 142°, identical with that isolated as a byproduct during the synthesis of ethyl 4-aminothieno[2,3-d]pyrimidine-6-carboxylate (Table 8, Chapter XI).

TABLE 11

4-(Substituted amino)thieno[2,3-d]pyrimidines

(144)



NR_2	X	Yield (%)	M.P.	Method	Halide used	Found (%)			Required (%)		
						C	H	N	C	H	N
I	II	III	IV	V	VI	VII			VIII		
$N(CH_2)_4$	$COPh$	90	190°	c	$BrCH_2COPh$	66.0	4.9	13.7	66.0	4.9	13.6
"	$COC_6H_4Br_1(p)$	80	190	c	$BrCH_2COC_6H_4Br(p)$	52.2	3.7	10.8	52.6	3.6	10.8
"	CO_2Et	70	160	c	$ClCH_2CO_2Et$	56.1	5.5	15.1	56.3	5.4	15.1
"	CN	60,40	185	d,e	$ClCH_2CN$	57.0	4.4	24.7	57.4	4.4	24.3
"	$CONH_2$	40	250	e	"	52.9	5.0	22.3	53.2	4.8	22.6
$NHCH_2Ph$	CO_2Et	80	145	e	$ClCH_2CO_2Et$	61.3	4.8	13.4	61.3	4.8	13.6
NHMe	$COPh$	85	195(d)	d	$BrCH_2COPh$	62.0	4.1	15.7	62.4	4.1	15.6

* See Table 8

continued/

Table 11 (continued)

I	II	III	IV	V	VI	VII			VIII		
NMe	COPh	80	180	d	$BrCH_2COPh$	63.5	4.7	15.0	63.6	4.6	14.8
NMe_2	"	80	175	e	"	63.9	4.6	15.0	63.6	4.6	14.8
$N(CH_2)_5$	"	75	151	d	"	67.8	5.7	12.5	67.7	5.6	12.5
$NCMe_2$	"	60	175	e	"	64.4	4.5	14.3	65.0	4.4	14.2

CHAPTER XIII

SYNTHESES OF POLYCHLOROPYRIMIDINE-5-CARBONITRILES AND REACTIONS OF POLYCHLOROPYRIMIDINE-5-CARBALDEHYDES AND 5-CARBONITRILES

4,6-Dichloropyrimidine-5-carbaldoxime.- To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (20 g) in glacial acetic acid (25 ml), hydroxylamine hydrochloride (10 g) and water (5 ml) were added. The reaction mixture was warmed for a few minutes during which solution was obtained. The solution was diluted with water to the precipitation point and cooled in ice. The crystalline product was filtered off, washed with water and dried (18 g, 90%), m.p.100°(d). It was identical with that from a (different) published method.[193]

4,6-Dichloropyrimidine-5-carbonitrile[193].- A solution of 4,6-dichloropyrimidine-5-carbaldoxime (10 g) in thionyl chloride (25 ml) was heated under reflux for 3 hours. The excess of thionyl chloride was removed by distillation under reduced pressure; the residue was added to ice-water (50 g) and the precipitated product filtered off, washed with water and dried (8.5 g, 90%), m.p. 145°.

2,4,6-Trichloropyrimidine-5-carbaldoxime.- To a solution of 2,4,6-trichloropyrimidine-5-carbaldehyde (30 g) in glacial acetic acid (25 ml), hydroxylamine hydrochloride (25 g) and water (10 ml) were added. The reaction mixture was treated as described for the synthesis of 4,6-dichloropyrimidine-5-carbaldoxime. The crystalline product was filtered, washed with water and dried (25 g; 80%), m.p. 145°. (Found: C, 27.4; H, 1.0; N, 19.1. $C_5H_2N_3Cl_3O$ requires C, 26.5; H, 0.9; N, 18.9%).

2,4,6-Trichloropyrimidine-5-carbonitrile.- 2,4,6-Trichloropyrimidine-5-carbaldoxime (25 g) in thionyl chloride (50 ml) was treated as described in the preparation of 2,4-dichloropyrimidine-5-carbonitrile. The precipitated product was filtered off, washed with water and dried (20 g, 90%). Crystallisation from petroleum ether (b.p. 100-120°) gave the title compound m.p. 125°. (Found: C, 28.7; H, 0.0 ; N, 20.1. $C_5N_3Cl_3$ requires C, 28.3; H, 0.0; N, 20.1%).

Reaction of 4,6-dichloropyrimidine-5-carbaldehyde with methyl or ethyl thioglycolate

2,4-Bis-(methoxycarbonylmethylthio)pyrimidine-5-carbaldehyde.- This intermediate was prepared by the following three methods.

a) To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (5.6 g) in methanol (50 ml), anhydrous sodium carbonate (10 g) and methyl thioglycolate (6 g)

were added. The reaction mixture was stirred at room temperature for 18 hours. The solid was filtered off and the residue treated with water and stirred for a few minutes. The insoluble material was filtered, washed with water and crystallised from petroleum ether (b.p. 100-120°) to yield the title compound (8.2 g), m.p. 120°. (Found: C, 41.9; H, 3.7; N, 8.8. $C_{11}H_{12}N_2O_5S_2$ requires C, 41.8; H, 3.8; N, 8.9%).

b) To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (4.0 g) in dioxan (25 ml), triethylamine (4.0 g) and methyl thioglycolate (4.0 g) were added. The reaction mixture was stirred at 5° for 30 minutes, treated with cold water (50 ml) and the precipitated solid was filtered off and crystallised from petroleum ether (b.p. 100-120°) to give a product (7.0 g) identical with that isolated from method (a).

c) To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (4.0 g) in toluene (25 ml), triethylamine (4.0 g) and methyl thioglycolate (4.0 g) were added. The reaction mixture was stirred at room temperature for an hour then heated under reflux for a further hour. The solid formed during reflux was filtered from hot toluene, dried and treated with water. The insoluble material was filtered off and crystallised from toluene to give a product (2.0 g) identical with that isolated from method (a).

Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate.- This thienopyrimidine was prepared by the following two methods. (p.133)

d) As described in method (a) except that the reaction mixture was evaporated to dryness, the residue treated with water (50 ml) and stirred for a few minutes. The insoluble material was filtered off, washed with water and crystallised from methanol to give the title compound (8.5 g), m.p. 143°. (Found: C, 44.4; H, 3.4; N, 9.5. $C_{11}H_{10}N_2O_4S_2$ requires C, 44.9; H, 3.4; N, 9.4%).

e) As described in method (c), except that the reaction mixture was heated under reflux for 8 hours. The solid formed during reflux was filtered from the hot toluene and the filtrate was reduced in volume and allowed to cool. The crystalline product (6.0 g) was identical with that isolated in (d) above.

Ethyl 4-ethoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate.- To a solution of 4,6-dichloropyrimidine-5-carbaldehyde (7.0 g) in ethanol (30 ml), sodium carbonate (7.0 g) and ethyl thioglycolate (7.0 g) were added. The reaction mixture was stirred at room temperature for 18 hours then evaporated to dryness. The residue was treated with water (50 ml) and stirred for a few minutes. The insoluble material was filtered off, washed with water, followed by propan-2-ol, and crystallised from propan-2-ol, to give the title compound (7.5 g),

m.p. 93°. (Found: C, 48.3; H, 4.4; N, 8.8. $C_{13}H_{14}N_2O_4S_2$ requires C, 47.9; H, 4.3; N, 8.6%). (also see page 133)

Reaction of 4,6-dichloropyrimidine-5-carbonitrile with methyl thioglycolate

4,6-Bis-(methoxycarbonylmethylthio)pyrimidine-5-carbonitrile.- To a solution of 4,6-dichloropyrimidine-5-carbonitrile (3.2 g) in diethyl ether (50 ml), sodium carbonate (5 g) and methyl thioglycolate (3 g) were added. The reaction mixture was stirred at room temperature for 2 days and then evaporated to dryness. The residue was treated with water (50 ml) and stirred for a few minutes. The insoluble material was filtered and crystallised from toluene to give the title compound (2.5 g), m.p. 158°. (Found: C, 42.2; H, 3.5; N, 13.4. $C_{11}H_4N_3O_4S_2$ requires C, 42.2; H, 3.5; N, 13.4%).

Methyl 5-amino-4-methoxycarbonylmethylthiothieno-[2,3-d]pyrimidine-6-carboxylate.- This was obtained by direct synthesis from the dichloropyrimidine, or cyclisation of the intermediate isolated from above.(also see Table 13).

f) 4,6-Dichloropyrimidine-5-carbonitrile (5.6 g) in toluene (50 ml), triethylamine (5.0 g) and methyl thioglycolate (5.0 g) were treated as in method (e). The crystalline product (6.5 g), m.p. 171°. (Found: C, 42.2; H, 3.5; N, 13.4. $C_{11}H_{11}N_3O_4S_2$ requires C, 42.2; H, 3.5; N, 13.4%).

g) 4,6-Bis-(methoxycarbonylmethylthio)pyrimidine-5-carbonitrile (1.5 g) in toluene (10 ml) and triethylamine (0.5 g) were heated under reflux for 4 hours. The work-up procedure was as in method (e). The crystalline product (1.3 g) was identical with that isolated in (f).

Methyl 5-amino-4-methoxythieno[2,3-d]pyrimidine-6-carboxylate.- This thienopyrimidine was obtained unexpectedly by the following method.

h) 4,6-Dichloropyrimidine-5-carbonitrile (5.6 g) in methanol (50 ml), anhydrous sodium carbonate (10 g) and methyl thioglycolate (6 g) were stirred at room temperature for 2 hours. The reaction mixture was evaporated to dryness and the dark green residue treated with water (50 ml) and stirred for a few minutes. The insoluble material was filtered off and crystallised from petroleum ether (b.p. 100-120°) to give the title compound (7.0 g), m.p. 183°. (Found: C, 45.0; H, 3.7; N, 17.7. $C_9H_9N_3O_3S$ requires C, 45.2; H, 3.8; N, 17.6%).

Reaction of 2,4,6-Trichloropyrimidine-5-carbaldehyde with methyl thioglycolate

Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno-[2,3-d]pyrimidine-6-carboxylate.- This thienopyrimidine was prepared by two methods.

i) 2,4,6-Trichloropyrimidine-5-carbaldehyde (3.0 g) in methanol (25 ml), sodium carbonate (6.0 g) and methyl thioglycolate (6.0 g) were stirred at room temperature for 24 hours. The reaction mixture was evaporated to dryness and the residue treated with water (50 ml) and left to stir for a few minutes. The excess of thioglycolate and water were decanted leaving white sticky solid, when stirred in methanol (20 ml), gave solid which was filtered off and crystallised from petroleum ether (b.p. 100-120°) to give the title compound (2.5 g), m.p. 122°. (Found: C, 42.1; H, 3.5; N, 6.8. $C_{14}H_{14}N_2O_6S_3$ requires C, 41.8; H, 3.5; N, 6.9%).

j) 2,4,6-Trichloropyrimidine-5-carbaldehyde (8.5 g) in toluene (50 ml), triethylamine (8.0 g) and methyl thioglycolate (8.0 g) were treated as in method (e). The crystalline product (9.0 g) was identical with that isolated in method (i).

Reaction of 2,4,6-trichloropyrimidine-5-carbonitrile with methyl thioglycolate

2,4,6-Tris-(methoxycarbonylmethylthio)pyrimidine-5-carbonitrile.- 2,4,6-Trichloropyrimidine-5-carbonitrile (6 g) in diethyl eter (50 ml), sodium carbonate (12 g) and methyl thioglycolate (10 g) were stirred at room temperature for 18 hours. The sodium carbonate was filtered off and the filtrate was evaporated to near

dryness. The oily residue was washed with carbon tetrachloride (10 ml) and the precipitated solid was filtered off and crystallised from toluene to give the title compound (10 g), m.p. 86°. (Found: C, 40.3; H, 3.7; N, 9.9. $C_{14}H_{15}N_3O_6S_3$ requires C, 40.3; H, 3.6; N, 10.0%).

Methyl 5-amino-2,4-bis-(methoxycarbonylmethylthio)-thieno[2,3-d]pyrimidine-6-carboxylate.- This thienopyrimidine was prepared by the following two methods (also p.136)

k) 2,4,6-Trichloropyrimidine-5-carbonitrile (6 g) in toluene (25 ml), triethylamine (6 g) and methyl thioglycolate (9 g) were treated as in method (e). The crystalline product (7.5 g) was the title compound, m.p. 135°. (Found: C, 40.4; H, 3.6; N, 9.9. $C_{14}H_{15}N_3O_6S_3$ requires C, 40.3; H, 3.6; N, 10.0%).

l) 2,4,6-Tris-(methoxycarbonylmethylthio)pyrimidine-5-carbonitrile (4.0 g) in toluene (20 ml) and triethylamine (1 ml) were heated under reflux for 6 hours. The work-up procedure is as in method (e). The crystalline product was identical with that isolated in method (k).

Methyl 5-amino-4-methoxy-2-methoxycarbonylmethylthio-thieno[2,3-d]pyrimidine-6-carboxylate.- 2,4,6-Trichloropyrimidine-5-carbonitrile (1.5 g) in methanol (25 ml), sodium carbonate (5 g) and methyl thioglycolate (5 g) were stirred at room temperature for 2 days. The work-up procedure as in method (h). The insoluble solid was

filtered off and crystallised from methanol to give the title compound (2.5 g), m.p. 174°. (Found: C, 42.1; H, 3.8; N, 12.4. $C_{12}H_{13}N_3O_2S_2$ requires C, 42.0; H, 3.8; N, 12.2%).

Methyl 5-amino-2,4-dimethoxythieno[2,3-d]pyrimidine-6-carboxylate.- 2,4,6-Trichloropyrimidine-5-carbonitrile (3.0 g) in methanol (25 ml), sodium carbonate (6.0 g) and methyl thioglycolate (6.0 g) were stirred at 50° for 2 days. The work-up procedure as in method (h). The insoluble solid was filtered off and crystallised from aqueous ethanol to give the title compound (2.0 g), m.p. 210°. (Found: C, 44.3; H, 4.1; N, 15.4. $C_{10}H_{11}N_3O_4S$ requires C, 44.6; H, 4.1; N, 15.6%).

Some of the crude product (0.2 g) was crystallised from propan-2-ol to give mainly 2,4-dimethoxy-6-methoxycarbonylmethylthiopyrimidine-5-carbonitrile (0.1 g), m.p. 65° (d) (Found: C, 44.6; H, 4.1; N, 15.7. $C_{10}H_{11}N_3O_4S$ requires C, 44.6; H, 4.1; N, 15.6%) with a trace of the cyclised derivative as impurity.

CHAPTER XIV

SYNTHESES AND REACTIONS OF POLYMERCAPTOPYRIMIDINE-5-CARBONITRILES AND 5-CARBALDEHYDE

4,6-Dimercaptopyrimidine-5-carbaldehyde.- This was prepared by the following two methods.

a) 4,6-Dichloropyrimidine-5-carbaldehyde (7.0 g) and thiourea (7.0 g) in 80% aqueous ethanol (100 ml) were treated as described in method (a) (page 116). The product (4.5 g), m.p. > 215° (decomp). (Found: C, 33.7; H, 2.0; N, 15.6. $C_5H_4N_2OS_2$ requires C, 34.8; H, 2.0; N, 16.2%).

b) 4,6-Dichloropyrimidine-5-carbaldehyde (6.0 g) in methanol (25 ml) was treated with a methanolic solution of sodium hydrogen sulphide (25 ml) as described in method (b) (page 116). The product (5.3 g) was reprecipitated from an N,N-dimethylformamide solution (10 ml) by addition of water (5 ml) to give a product identical with that isolated in method (a) above.

4,6-Dimercaptopyrimidine-5-carbonitrile.- 4,6-Dichloropyrimidine-5-carbonitrile (1.7 g) in methanol (5 ml) was treated with methanolic sodium hydrogen sulphide (10 ml) as described in method (b) (page 116). The product (1.5 g), m.p. 250° (decomp). (Found: C, 35.4; H, 1.9; N, 24.0. $C_5H_3N_3S_2$ requires C, 35.5; H, 1.8; N, 24.8%).

2,4,6-Trimercaptopyrimidine-5-carbonitrile.- 2,4,6-Trichloropyrimidine-5-carbonitrile (3.4 g) in methanol (20 ml) and thiourea (5 g) in water (5 ml) were mixed and heated under reflux for 30 minutes. The work-up procedure was as in method (a) (page 116). The product (3.0 g) was reprecipitated from an N,N-dimethylformamide solution (10 ml) by addition of water (5 ml) to give a yellow solid, m.p. >200° (decomp). (Found: C, 29.5; H, 2.2; N, 27.0. $C_5H_3N_3S_3$ requires C, 29.6; H, 1.5; N, 20.9%). Though clearly impure, this compound gave the desired products in subsequent reactions.

Condensations of 2,4-dimercaptopyrimidine-5-carbaldehyde or 5-carbonitrile with halogeno compounds

The following three methods were used for the syntheses of thienopyrimidines listed in Tables 12 and 13.

c) To a solution of 4,6-dimercaptopyrimidine-5-carbaldehyde (or 5-carbonitrile) (0.01 mole) in methanol (25 ml) and triethylamine (5 ml), the appropriate halogeno compound (0.02 mole) was added. The reaction solution was stirred at room temperature for a few minutes when the product began to crystallise out. Stirring was continued for a further 2 hours. The solid was filtered off, washed with water, followed by methanol and crystallised from a suitable solvent.

d) As described in method (c) except that the reaction mixture was heated under reflux for 3 hours. Melting points, yields, halides used and elemental analyses of products are recorded in Tables 12 and 13.

Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate.- 4,6-Dimercaptopyrimidine-5-carbaldehyde (0.2 g) in methanol (10 ml), triethylamine (2 ml) and ethyl chloroacetate (1.0 g) were treated as in method (d). Transesterification took place to give the title compound, identical with that isolated in method (d) (page 125).

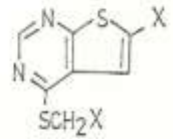
Ethyl 4-ethoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate.- 4,6-Dimercaptopyrimidine-5-carbonitrile (0.2 g) in ethanol (10 ml), triethylamine (2 ml) and ethyl chloroacetate (1.0 g) were treated as in method (d) above. The product was identical with that previously isolated (page 125).

Ethyl 5-amino-4-ethoxycarbonylmethylthiothieno-[2,3-d]pyrimidine-6-carboxylate.- 4,6-Dimercaptopyrimidine-5-carbonitrile (0.2 g), ethanol (10 ml), triethylamine (2 ml) and ethyl chloroacetate (1 ml) were stirred at room temperature for 30 minutes. Water (15 ml) was added and stirring continued for a further few minutes. The precipitated product was filtered off and crystallised from ethanol to give the title compound, m.p. 100°. (See Table 13).

TABLE 12

4-(Substituted methylthio)thieno[2,3-d]pyrimidines

(173)



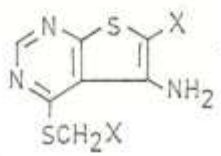
X	Yield %	M.P.	Crystn. solvent	Method	Halide used	Found (%) C	H	N	Required (%) C	H	N
CO_2Me	90	143°	MeOH	d	$ClCH_2CO_2Me$	44.4	3.4	9.5	44.9	3.4	9.4
CO_2Et	90	93	EtOH	-	$ClCH_2CO_2Et$	48.3	4.4	8.8	47.9	4.3	8.6
COPh	80,80	160	MeOH	c,d	$BrCH_2COPh$	61.6	3.6	7.6	61.2	3.9	6.9
$COC_6H_5Br(p)$	90,90	177	dioxan	c,d	$BrCH_2COC_6H_5Br(p)$	46.4	2.7	4.7	46.3	2.2	5.1

c see page 125.

TABLE 13

5-Amino-4-(substituted methylthio)thieno[2,3-d]pyrimidines

(177)



X	Yield %	M.P.	Crystn. solvent	Method	Halide used	Found (%) C	H	N	Required (%) C	H	N
CO_2Me [a]	90	171°	MeOh	c	$ClCH_2CO_2Me$	42.2	3.5	13.4	42.2	3.5	13.4
CO_2Et	90	100	EtOH	-	$ClCH_2CO_2Et$	45.8	4.5	12.4	45.7	4.4	12.3
COMe	90	200	MeOH	c	$ClCH_2COMe$	46.6	4.0	14.8	46.9	3.9	14.9
COPh	90,90	188	MeOH	c,d	$ClCH_2COPh$ or $BrCH_2COPh$	61.9	3.7	10.3	62.2	3.7	10.4
$COC_6H_4Br(P)$	90	215	MeOH	c	$BrCH_2COC_6H_4Br(P)$	44.8	2.3	7.4	44.8	2.3	7.5
$CONH_2$	80,90	250	Toluene; MeOH	c,d	$ClCH_2CONH_2$	38.0	3.2	24.6	38.1	3.2	24.8
CN	90	220	MeOH	c	$ClCH_2CN$	43.4	2.1	27.6	43.7	2.0	28.3

[a] see page 126

Methyl 5-amino-2,4-bis-(methoxycarbonylmethylthio)thieno-[2,3-d]pyrimidine-6-carboxylate.- 2,4,6-Trimercapto-pyrimidine-6-carbonitrile (0.3g), methanol (5 ml), triethylamine (0.4 g) and methyl thioglycolate (0.4 g) were heated under reflux for 5 minutes then cooled. The crystallised solid was filtered, washed with water and recrystallised from toluene to give a product (0.3 g) identical with that isolated in method (k) (page 129).

5-Amino-4-Phenacylthiothieno[2,3-d]pyrimidin-6-yl phenyl ketone.- 2,4,6-Trimercaptopyrimidine-5-carbonitrile (0.2 g), methanol (5 ml), triethylamine (0.6 g) and phenacyl bromide (0.6 g) were heated under reflux for 5 minutes. After cooling, the crystalline product was filtered off, washed with water, followed by methanol and dried (0.4 g), m.p. 165° (decomp). (Found: C, 62.3; H, 3.8; N, 8.0. $C_{29}H_{21}N_3O_3S_3$ requires C, 62.7; H, 3.8; N, 7.7%).

CHAPTER XV

REACTIONS OF SOME THIENO[2,3-d]PYRIMIDINES

Syntheses of 2-methylthiothienopyrimidines

4,6-Bis-(methoxycarbonylmethylthio)-2-methylthiopyrimidine-5-carbaldehyde.- To a solution of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (5.0 g) in toluene (50 ml), triethylamine (5 g) and methyl thioglycolate (4.5 g) were added. The reaction mixture was stirred at room temperature for 16 hours then heated under reflux for a further 2 hours. The solid formed during reflux was filtered off from hot toluene and the filtrate cooled to give a crystalline product (4.0 g), m.p. 107° (Found: C, 40.1; H, 4.0; N, 7.6. $C_{12}H_{14}N_2O_5S_3$ requires C, 39.8; H, 3.9; N, 7.7%). The toluene filtrate was kept for the cyclisation reaction below.

Methyl 4-methoxycarbonylmethylthio-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate.- To the toluene mother liquor from the reaction above, 4,6-bis-(methoxycarbonylmethylthio)-2-methylthiopyrimidine (2.0 g) and triethylamine (2.0 g) were added. The reaction mixture was heated under reflux for 6 hours and the solid formed during reflux was filtered from the hot toluene. The filtrate was reduced in volume and allowed to cool to give a crystalline product (3.5 g), m.p. 136° (Found: C, 42.1; H, 3.7; N, 8.1. $C_{12}H_{12}N_2O_4S_3$ requires C, 41.9;

H, 3.5; N, 8.1%).

Methyl 5-amino-4-methoxycarbonylmethylthio-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate.- 4,6-Dichloro-2-methylthiopyrimidine-5-carbonitrile (3.6 g), toluene (50 ml), triethylamine (4 g) and methyl thioglycolate (4 g) were heated under reflux for 8 hours. The solid formed during reflux was filtered from hot toluene and the filtrate was allowed to cool to give a crystalline product (4.0 g), m.p. 194° (Found: C, 40.6; H, 3.9; N, 11.4. $C_{12}H_{13}N_3O_4S_3$ requires C, 40.1; H, 3.6; N, 11.7%).

Methyl 2-methoxycarbonylmethylthio-4-methylthiothieno[2,3-d]pyrimidine-6-carboxylate.- This was prepared from two different starting materials by methods (a) and (b).

a) Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno-[2,3-d]pyrimidine-6-carboxylate (0.7 g) was added to a stirred methanolic solution of sodium methyl mercaptide (10 ml) (prepared by passing methyl mercaptan through a cooled and stirred solution of 2N-sodium methoxide in methanol until the pH was 8). After 10 minutes during which solution was obtained followed by precipitation of a solid the product was filtered off, washed with methanol and crystallised from propan-2-ol to give the title compound (0.4 g), m.p. 130° (Found: C, 42.1; H, 3.6; N, 8.1. $C_{12}H_{12}N_2O_4S_3$ requires C, 41.9; H, 3.5; N, 8.1%).

b) To a solution of methyl 4-mercapto-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate (0.1 g) (prepared as described below) in methanol (5 ml) and triethylamine (0.5 g), methyl iodide (0.5 g) was quickly added and the reaction solution was stirred at room temperature for 30 minutes. The solid was filtered off, washed with water and crystallised from propan-2-ol to give a product (0.1 g) identical with that isolated in method (a).

Methyl 4-mercapto-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate.- Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (3.0 g) was stirred in a methanolic solution of sodium hydrogen sulphide (25 ml)[prepared as in method (b) (page 116)] at room temperature for 2 hours. The reaction mixture was acidified with 2N-hydrochloric acid and the precipitated solid was filtered off, washed with water and crystallised from methanol to give the title compound (2.0 g), m.p. 205° (Found: C, 39.7; H, 2.9; N, 8.6. $C_{11}H_{10}N_2O_4S_3$ requires C, 40.0; H, 3.0; N, 8.5%).

Methyl 2,4-bis-(methylthio)thieno[2,3-d]pyrimidine-6-carboxylate.- This was prepared from two different starting materials by methods (c) and (d).

c) As in method (a) (page 138) except that the reaction mixture was kept at room temperature

for 1 hour. The solid was crystallised from methanol to give the title compound (0.3 g), m.p. 143° (Found: C, 41.8; H, 3.4; N, 9.6. $C_{10}H_{10}N_2O_2S_3$ requires C, 41.9; H, 3.5; N, 9.8%).

d) Methyl 4-methoxycarbonylmethylthio-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate (0.7 g) was treated as in method (a) except the reaction was allowed to proceed for 30 minutes at room temperature. The solid crystallised from methanol to give a product (0.35 g) identical with that isolated in method (c).

Methyl 2-methylthio-4-piperidinothieno[2,3-d]-pyrimidine-6-carboxylate.- This was prepared from two different starting materials by the methods (e) and (f).

e) Methyl 4-methoxycarbonylmethylthio-2-methylthiothieno[2,3-d]-pyrimidine-6-carboxylate (2.0 g) in neat piperidine (10 ml) was stirred at room temperature for 30 minutes during which solution was obtained followed by precipitation of a solid. The reaction mixture was treated with water (50 ml) and stirred for a few minutes. The solid was filtered off, washed with water and crystallised from propan-2-ol to give the title compound (1.6 g), m.p. 135° (Found: C, 51.8; H, 5.3; N, 13.2. $C_{14}H_{17}N_3O_2S_2$ requires C, 52.0; H, 5.3; N, 13.0%).

f) Methyl 2,4-bis-methylthiothieno[2,3-d]pyrimidine-6-carboxylate (0.1 g) was treated with piperidine (2 ml) as described in method (e) above. The solid was crystallised from propan-2-ol to give a product identical with that isolated in method (e).

Methyl 2-methoxycarbonylmethylthio-4-piperidinothieno[2,3-d]pyrimidine-6-carboxylate.- This was prepared from two different thienopyrimidines by the methods (g) and (h).

g) Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno-[2,3-d]pyrimidine-6-carboxylate (0.8 g) in neat piperidine (5 ml) was stirred for 5 minutes until solution was obtained (slight warming may be necessary). The reaction solution was treated with cold water (25 ml) and the precipitated white solid was filtered off, washed with water and crystallised from petroleum ether (b.p. 100-120°) to give the title compound (0.6 g) m.p. 141° (Found: C, 50.2; H, 5.1; N, 11.1. $C_{16}H_{19}N_3O_4S_2$ requires C, 50.4; H, 5.0; N, 11.0%).

h) Methyl 2-methoxycarbonylmethylthio-4-methylthiothieno[2,3-d]pyrimidine-6-carboxylate (0.1 g) in neat piperidine (1 ml) was treated as in method (g). The solid crystallised from propan-2-ol to give a product (0.1 g) identical with that isolated in method (g).

4-Mercapto-2-methoxycarbonylmethylthio-6-piperidinocarbonylthieno[2,3-d]pyrimidine.- Methyl 4-mercapto-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate (1.0 g) in neat piperidine (5 ml) was boiled for 5 minutes during which time a dark green solution was obtained. The excess of piperidine was evaporated and the residue treated with cold water (15 ml) and stirred for a few minutes. The solution was acidified with 2N-hydrochloric acid and the yellow solid was filtered off and crystallised from methanol to give the title compound (1.0 g), m.p. 210° (decomp) (Found: C, 46.9; H, 4.5; N, 11.0. $C_{15}H_{17}N_3O_3S_3$ requires C, 47.0; H, 4.4; N, 11.0%).

2,4-Bis-(methoxycarbonylmethylthio)-6-piperidinocarbonylthieno[2,3-d]pyrimidine.- To a solution of the above amide (0.1 g) in methanol (10 ml) and triethylamine (0.5 g), methyl chloroacetate (0.5 g) was added. The reaction solution was heated under reflux for 30 minutes and then evaporated to near dryness. The residue was treated with cold water (15 ml) and the solution stirred for a few minutes. The water was decanted off and the sticky solid treated with methanol (5 ml). The solid was filtered off and crystallised from methanol to give the title compound (0.1 g), m.p. 118° (Found: C, 47.3; H, 4.6; N, 9.2. $C_{18}H_{21}N_3O_5S_3$ requires C, 47.5; H, 4.6; N, 9.2%).

2-Methoxycarbonylmethylthio-4-piperidino-6-piperidinocarbonylthieno[2,3-d]pyrimidine.- This was prepared from two different starting materials by methods (i) and (j).

i) Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno-[2,3-d]pyrimidine-6-carboxylate (0.8 g) in neat piperidine (10 ml) was heated under reflux for 2 hours. The reaction solution was evaporated to near dryness and the residue treated with ice-water (25 g) and stirred for a few minutes. The solid was filtered off, washed with water and crystallised from petroleum ether (b.p. 100-120°) to give the title compound (0.7 g), m.p. 244° (Found: C, 54.3; H, 5.9; N, 13.6. $C_{20}H_{26}N_4O_3S_2$ requires C, 55.3; H, 6.0; N, 13.0%).

j) 2,4-Bis-(methoxycarbonylmethylthio)-6-piperidino-carbonylthieno[2,3-d]pyrimidine (0.1 g) (page 142) in neat piperidine (2 ml) was heated under reflux for 30 minutes. The reaction mixture was treated with cold water (10 ml) and stirred for a few minutes before the solid was filtered off and crystallised from petroleum ether (b.p. 100-120°) to give a product (0.05 g) identical with that isolated in method (i).

Methyl 4-morpholino-2-methoxycarbonylmethylthio-thieno[2,3-d]pyrimidine-6-carboxylate.- Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (1.0 g) in neat morpholine (5 ml) was

heated under reflux for 30 minutes. The reaction mixture was treated with cold water (50 ml) and stirred for a few minutes. The aqueous solution was decanted off and the sticky solid treated with propan-2-ol, filtered off and crystallised from propan-2-ol to give the title compound (0.4 g), m.p. 155° (Found: C, 47.0; H, 4.6; N, 11.2. $C_{15}H_{17}N_3O_5S_2$ requires C, 47.0; H, 4.4; N, 11.0%).

The aqueous solution which had been decanted off was stirred for another 15 minutes during which a solid precipitated. This was filtered off and crystallised from water to give 4-morpholino-6-morpholinocarbonyl-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine (0.2 g) m.p. 215° (Found: C, 47.5, H, 4.9; N, 12.3. $C_{18}H_{22}N_4O_5S_2$ requires C, 47.4; H, 5.3; N, 12.3%).

4-Benzylamino-6-benzylaminocarbonyl-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine.- Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (1.5 g), toluene (20 ml), triethylamine (2.0 g) and benzylamine (1.0 g) were heated under reflux for 20 minutes. The reaction mixture was evaporated to dryness and the residue was treated with water. The resulting solid was filtered off and crystallised from methanol to give the title compound (0.9 g), m.p. 175° (Found: C, 57.3; H, 4.5; N, 11.1. $C_{24}H_{22}N_4O_3S_2$, H_2O requires C, 58.0; H, 4.8; N, 11.3%).

4-Hydrazino-6-hydrazinocarbonyl-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine.- Methyl 2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (0.8 g), ethanol (20 ml), triethylamine (1.0 g) and hydrazine hydrate (0.8 g) were heated under reflux, for 30 minutes. The solid formed during this time was filtered off and crystallised from water to give the title compound (0.4 g), m.p. 170° (Found: C, 36.7; H, 3.6; N, 24.2. $C_{10}H_{12}N_6O_3S_2$ requires C, 36.6; H, 3.7; N, 25.0%).

Methyl 2,4-dipyrrolidinothieno[2,3-d]pyrimidine-6-carboxylate.- Methyl 2,4-bis-(methoxycarbonylmethylthio)-thieno[2,3-d]pyrimidine-6-carboxylate (1.0 g) in neat pyrrolidine (5 ml) was heated under reflux for 30 minutes. The reaction mixture was treated with cold water (50 ml) and stirred for a few minutes before the solid was filtered off and crystallised from a mixture of propan-2-ol and petroleum ether (b.p. 100-120°) to give the title compound (0.6 g), m.p. 269° (decomp) (Found: C, 58.1; H, 6.3; N, 16.7. $C_{16}H_{20}N_4O_2S$ requires C, 57.8; H, 6.0; N, 16.9%).

2,4-Dipyrrolidino-6-pyrrolidinocarbonylthieno-[2,3-d]pyrimidine.- As above except that the reaction mixture was refluxed for 3 hours. The solid was crystallised from propan-2-ol to give the title compound (0.4 g), m.p. 250° (decomp) (Found: C, 60.5; H, 7.0; N, 18.1. $C_{19}H_{25}N_5OS$ requires C, 61.4; H, 6.7; N, 18.8%).

Ethyl 2,4-diethoxythieno[2,3-d]pyrimidine-6-carboxylate.- Methyl 2,4-bis-(methoxycarbonylmethylthio)thienopyrimidine-6-carboxylate (1.0 g) was added to an ethanolic solution of sodium ethoxide (25 ml) [sodium (0.5 g) in ethanol (25 ml)] and heated under reflux for one hour. The insoluble material was filtered off and the ethanolic filtrate was treated with water (25 ml) to give a solid which was filtered off and crystallised from 50% aqueous ethanol. The title compound (0.25 g) had m.p. 120° (Found: C, 52.2; H, 5.5; N, 9.3. $C_{13}H_{16}N_2O_4S$ requires C, 52.7; H, 5.4; N, 9.5%).

Methyl 4-methoxy-2-methoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate.- The same starting material as in the previous experiment (1.0 g) was added to a methanolic solution of sodium methoxide (25 ml) [sodium (0.5 g) in methanol (25 ml)] and heated under reflux for 10 minutes during which time solution was obtained and a product crystallised out. The solid was filtered off and recrystallised from methanol to give the title compound (0.5 g), m.p. 98° (Found: C, 43.7; H, 3.6; N, 8.4. $C_{12}H_{12}N_2O_5S_2$ requires C, 43.9; H, 3.7; N, 8.5%).

Reactions of Methyl 5-amino-2,4-bis-(methoxycarbonylmethylthio)thieno[2,3-d]pyrimidine-6-carboxylate (165)

This amine was the starting material in the next four preparations.

Methyl 5-amino-2-methoxycarbonylmethylthio-4-piperidinothieno[2,3-d]pyrimidine-6-carboxylate.- The amine (165) (1.0 g) in piperidine (10 ml) was stirred at room temperature for one hour. The reaction solution was treated with cold water (50 ml) and stirred for a further 10 minutes after which the solid was filtered off and crystallised from petroleum ether (b.p. 100-120°) to give the title compound (0.6 g), m.p. 125° (Found: C, 48.9; H, 5.2; N, 14.1. $C_{16}H_{20}N_4O_4S_2$ requires C, 48.5; H, 5.1; N, 14.1%).

5-Amino-2-methoxycarbonylmethylthio-4-pyrrolidino-thieno[2,3-d]pyrimidine-6-pyrrolidino carboxamide.- The same amine (165) (1.0 g) in pyrrolidine (5 ml) was heated at 50° for 10 minutes and the resulting solution was treated with cold water (25 ml) and stirred for a few minutes. The solid was filtered off and crystallised from toluene to give the title compound (0.8 g), m.p. 206° (Found: C, 50.2; H, 5.2; N, 16.7. $C_{18}H_{23}N_5O_3S_2$ requires C, 51.3; H, 5.5; N, 16.6%).

Methyl 5-amino-2,4-bis-methylthiothieno[2,3-d]-pyrimidine-6-carboxylate.- The same amine (165) (0.1 g) in a methanolic solution of sodium methyl mercaptide (25 ml) [prepared as in method (a) (page 138)] was stirred at room temperature for 12 hours. The solid was filtered off, washed with water, followed by methanol and crystallised from toluene to give the title compound (0.5 g) m.p. 214° (Found: C, 39.9; H, 3.7; N, 13.9. $C_{10}H_{11}N_3O_2S_3$ requires C, 39.9; H, 3.7; N, 14.0%).

Ethyl 5-amino-2,4-diethoxythieno[2,3-d]pyrimidine-6-carboxylate.- The same amine (165) (1.0 g) in an ethanolic solution of sodium ethoxide (20 ml) sodium (0.5 g) in ethanol (20 ml) was heated under reflux for one hour during which time a solution was obtained and a product precipitated. The reaction mixture was cooled and treated with water (20 ml). The solid was filtered off and crystallised from ethanol to give the title compound (0.4 g), m.p. 120° (Found: C, 52.2; H, 5.5; N, 9.3. $C_{13}H_{16}N_2O_4S$ requires C, 52.7; H, 5.4; N, 9.5%).

Reactions of 2-unsubstituted thienopyrimidines

1. With Amines

k) The appropriate alkyl 4-alkoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate (0.01 mole) and the amine (10 ml) were heated at 50° for 2 hours. The resulting solution was treated with ice water (50 g) and stirred for a few minutes before the precipitated solid was filtered off, washed with water and crystallised from a suitable solvent to give 4-substituted amino derivative (Tables 14-16).

l) Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate (1.5 g), ethanol (20 ml) and hydrazine hydrate (1.0 g) were heated under reflux for 2 hours during which time a solution was slowly obtained and a solid began to precipitate.

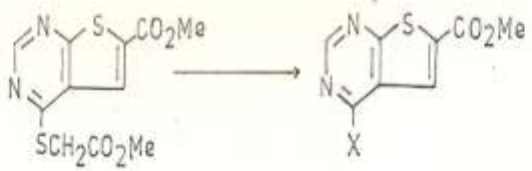
The reaction mixture was cooled and the crystalline product was filtered off, washed with water and recrystallised from ethanol to give methyl 4-hydrazinothieno[2,3-d]pyrimidine-6-carboxylate (0.8 g), m.p. 205° (see Table 14).

m) A solution of ethyl 4-ethoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate (1.6 g) in dioxan (10 ml) and pyrrolidine (1.0 g) were stirred at room temperature for one hour. The reaction mixture was treated with cold water (25 ml) and stirred for a few minutes. The solid was filtered off and crystallised from petroleum ether (b.p. 100-120°) to give ethyl 4-pyrrolidinothieno[2,3-d]pyrimidine-6-carboxylate (1.2 g), m.p. 159° (see Table 15).

n) The appropriate alkyl 4-alkoxycarbonylmethylthiothieno[2,3-d]pyrimidine-6-carboxylate (0.01 mole) and the neat amine (10 ml) were heated at 95° for 3 hours. The resulting solution was evaporated to near dryness, the residue treated with cold water (50 ml), and stirred for a few minutes. The solid was filtered off and crystallised from a suitable solvent to give a 4-(substituted amino)-thieno[2,3-d]pyrimidine-6-substituted carboxamide (see Table 17).

TABLE 14

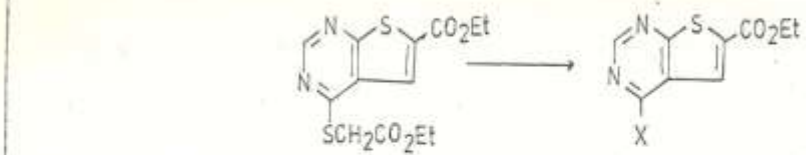
Methyl 4-substituted thieno[2,3-d]pyrimidine-6-carboxylates



X	Yield %	m.p.	Crystn. Solvent	Method	Found % C H N	Required C H N
NHPh	90	209°	propan-2-ol	k	58.7 4.0 14.4	58.9 3.9 14.7
N(CH2)5	90	105	Petroleum ether (b.p. 100-120°)	k	56.1 5.5 15.2	56.3 5.4 15.2
N(CH2)2O(CH2)2	80	150	"	k	50.8 4.7 14.4	51.6 4.7 15.0
NHNH2	95	205	EtOH	l	42.0 3.6 25.0	42.8 3.6 25.0
OPh	95	150	MeOH	o	48.5 3.7 12.4	48.2 3.6 12.5
SPh	95	195	Propan-2-ol	s	44.9 3.4 11.7	45.0 3.4 11.7
OH	80	>260(d)	"	u	42.4 2.7 12.3	42.5 2.7 12.4

TABLE 15

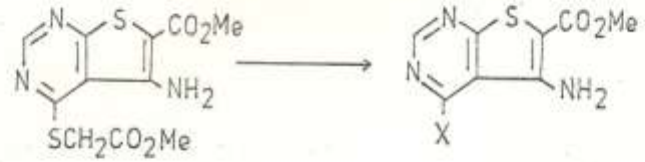
Ethyl 4-substituted thieno[2,3-d]pyrimidine-6-carboxylates



X	Yield %	m.p.	Crystn. Solvent	Method	Found % C	H	N	Required C	H	N
NHPh	85	217°	H_2O	k	62.4	4.8	33.5	62.9	4.8	33.3
$N(CH_2)_4$	95	159	Petroleum-ether (b.p. 100-120°)	m	56.1	5.5	15.1	56.3	5.4	15.2
$N(CH_2)_5$	80	83	"	k	57.6	5.8	14.4	57.7	5.8	14.4
$N(CH_2)_2O(CH_2)_2$	85	128	"	k	54.1	5.4	14.3	53.3	5.1	14.3
OEt	95	116	H_2O/EtOH	p	52.2	4.8	11.2	52.4	5.0	11.1

TABLE 16

Methyl 5-amino-4-substitutedthieno[2,3-d]pyrimidine-6-carboxylates

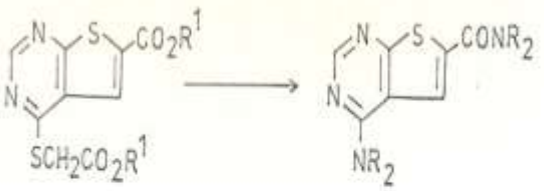


X	Yield %	m.p.	Crystn. Solvent	Method	Found % C	H	N	Required C	H	N
$NH(CH_2)_5$	95	210°	Petroleum-ether (b.p. 100-120°)	k	53.3	5.6	18.9	53.4	5.5	19.2
OMe	95	183	MeOH	o	45.0	3.7	17.7	45.2	3.8	17.6
SMe	95	219	"	t	42.2	3.5	16.6	42.4	3.5	16.5
OEt[a]	90	127	EtOH	p	48.9	4.9	15.6	49.4	4.9	15.7[a]

[a] The product was a 6-ethoxycarbonyl derivative

TABLE 17

4-(Substituted amino)thienopyrimidine-6-carboxamides



NR_2	R^1	Yield %	m.p.	Crystn. Solvent	Found % C	H	N	Required C	H	N
NMe_2	Me	95	300°	H_2O/MeOH	48.4	4.5	25.3	48.6	4.5	25.2
$NHCH_2Ph$	"	70	190	Petroleum ether (b.p. 100-120°)	65.2	4.9	14.5	65.3	5.1	14.3
NHC_6H_{11}	"	70	173	"	63.7	7.3	15.6	63.2	7.5	14.8
$N(CH_2)_4$	Me or Et	90,80	180	"	56.8	5.5	17.4	56.3	6.2	17.5
$NHNH_2$	Me or Et	90,95	262	D.M.F.	37.5	3.6	37.3	37.5	3.6	37.5
$NHCH_2CH_2OH$	Me	95	235	Petroleum ether (b.p. 100-120°)	46.7	5.0	19.8	46.8	5.0	19.9

2. With oxygen nucleophiles

o) The appropriate 4-methoxycarbonylmethylthiothieno-pyrimidine (0.01 mole) in 2N-methanolic sodium methoxide (25 ml) was heated under reflux for 10 minutes. The product was filtered off, washed with methanol and recrystallised from methanol to give the 4-methoxy derivative (Tables 14 and 16).

p) Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate (or its 5-amino analogue) (0.7 g) in 2N-ethanolic sodium ethoxide (25 ml) was heated under reflux for 10 minutes. The product was filtered off, washed with water and recrystallised from ethanol to give the ethyl 4-ethoxy-6-carboxylate derivative, (see Tables 15 and 16).

4-Hydroxythieno[2,3-d]pyrimidine-6-carboxylic acid.-

q) Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate (1.5 g) and 2N-sodium hydroxide (25 ml) were stirred at room temperature for 2 hours. The resulting solution was left to stand for a further 30 minutes before the precipitated sodium salt was filtered off, washed with acetone and dissolved in the minimum amount of water. The aqueous solution was acidified with 2N-hydrochloric acid; the yellow solid was filtered off, washed with water and dried to give

the title compound (0.7 g), m.p. > 260° (Found: C, 36.4; H, 3.2; N, 12.2. $C_7H_4N_2O_3S\ 2H_2O$ requires C, 36.2; H, 3.4; N, 12.1%).

4-Carboxymethylthiothieno[2,3-d]pyrimidine-6-carboxylic acid.-

r) Ethyl 4-ethoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate (1.1 g) in ethanol (25 ml), dioxan (5 ml) and 2N-sodium hydroxide (5 ml) were stirred at room temperature for 10 minutes. The precipitated solid was filtered off, dissolved in the minimum amount of water and acidified with 2N-hydrochloric acid to give the title compound (0.8 g), m.p. > 220° (decomp) (Found: C, 39.9; H, 2.4; N, 10.5. $C_9H_6N_2O_4S_2$ requires C, 40.0; H, 2.2; N, 10.4%).

3. With sulphur nucleophiles

s) Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate (3.0 g) in a methanolic solution of sodium methyl mercaptide (25 ml) [prepared as in method (a)] was stirred at room temperature for 2 hours. The resulting solution was treated with cold water (25 ml) before the precipitated solid was filtered, washed with methanol and crystallised from methanol to give methyl 4-methylthiothieno[2,3-d]pyrimidine-6-carboxylate (2.3 g), m.p. 195° (see Table 14).

t) The 5-amino analogue of the starting material used in method (s) (1.0 g) in a methanolic solution of sodium methyl mercaptide (25 ml) was stirred at room temperature for 10 minutes. The precipitated solid from the reaction solution was filtered off, washed with water and crystallised from methanol to give the 4-methylthio derivative (0.8 g) (see Table 16).

u) Methyl 4-methoxycarbonylmethylthiothieno[2,3-d]-pyrimidine-6-carboxylate (3.5 g) in a methanolic solution of sodium hydrogen sulphide (25 ml) [prepared as in method (b) (page 116)] was stirred at room temperature for 3 hours. The insoluble material was filtered off before the filtrate was acidified with 2N-hydrochloric acid. The precipitated solid was filtered off, washed with water and crystallised from propan-2-ol to give the 4-mercapto derivative (2.0 g), (see Table 14).

5-Amino-4-pyrrolidinothieno[2,3-d]pyrimidine-6-carbonamide.- 5-Amino-4-aminocarbonylmethylthiothieno-[2,3-d]pyrimidine-6-carbonamide (0.3 g), methanol (5 ml) and pyrrolidine (0.5 g) were boiled for 2 minutes. The reaction mixture was evaporated to dryness, the residue treated with water (5 ml) and the solid filtered off and crystallised from petroleum ether (b.p. 100-120°)

to give the title compound (0.1 g), m.p. 205° (Found: C, 46.3; H, 5.4; N, 25.8. $C_{11}H_{13}N_5OS\ H_2O$ requires C, 46.9; H, 5.3; N, 25.0%).

5-Amino-4-mercaptothieno[2,3-d]pyrimidine-6-carbonamide.- The starting material used in the above experiment (0.3 g) in a methanolic solution of sodium hydrogen sulphide (5 ml) [prepared as in method (b) (page 116)] was stirred at room temperature for 30 minutes. The reaction mixture was acidified with 2N-hydrochloric acid and the precipitated solid purified by reprecipitation from alkaline solution to give the title compound (0.1 g), m.p. > 230° (Found: C, 35.1; H, 2.6; N, 22.1. $C_7H_7N_4OS_2\ H_2O$ requires C, 34.5; H, 3.0; N, 22.4%).

5-Amino-4-methoxythieno[2,3-d]pyrimidine-6-carbonamide.- The starting material used in the above experiment (0.2 g) in a 2N-methanolic sodium methoxide (5 ml) was boiled for 5 minutes. The precipitated solid was filtered off, washed with water and crystallised from methanol to give the title compound (0.1 g), m.p. 200° (decomp) (Found: C, 42.2; H, 3.6; N, 25.0. $C_8H_8N_4O_2S$ requires C, 42.8; H, 3.6; N, 25.0%).

8-(2-Chloroethylaminocarbonyl)imidazo[1,2-c]-thieno[3,2-e]pyrimidine hydrochloride (209).- 4-(2-Hydroxyethylamino-6-(2-hydroxyethylaminocarbonyl)thieno-[2,3-d]pyrimidine (2.0 g) in thionyl chloride (10 ml) was heated under reflux for 30 minutes. The resulting solution was poured into ice and the precipitated solid was filtered off and left to dry under vacuum for 12

hours to give the title compound (2.0 g), m.p. 250° (Found: C, 38.7; H, 4.1; N, 16.4. $C_{11}H_{11}N_4OClS_2OHCl$ requires C, 39.1; H, 4.1; N, 16.6%).

Methyl tetrazolo[1,5-c]thieno[3,2-e]pyrimidine-8-carboxylate (212).- Methyl 4-hydrazinothieno[2,3-d]-pyrimidine-6-carboxylate (0.8 g), glacial acetic acid (10 ml), sodium nitrite (0.6 g) and water (2.0 g) were stirred at room temperature for one hour. The reaction mixture was treated with cold water (100 ml) and the precipitated solid was filtered off and crystallised from aqueous acetic acid to give the title compound (0.7 g), m.p. 168° (Found: C, 40.6; H, 2.2; N, 29.7. $C_8H_5N_5O_2S$ requires C, 40.9; H, 2.1; N, 29.8%).

Methyl 4-(2-formylhydrazino)thieno[2,3-d]pyrimidine-6-carboxylate.- Methyl 4-hydrazinothieno[2,3-d]-pyrimidine-6-carboxylate (0.8 g) in 98% formic acid (10 ml) was heated under reflux for 30 minutes. The reaction mixture was treated with water (50 ml) and stirred for a few minutes. The precipitated solid was filtered off and crystallised from water to give the title compound (0.7 g), m.p. 268° (Found: C, 41.0; H, 3.3; N, 21.4. $C_9H_8N_4O_3S\frac{1}{2}H_2O$ requires C, 41.4; H, 3.4; N, 21.5%).

Methyl 4-hydroxy-5-nitrothieno[2,3-d]pyrimidine-6-carboxylate.- Methyl 4-methoxycarbonylmethylthio-thieno[2,3-d]pyrimidine-6-carboxylate (4.0 g) was gradually added to a stirred and cooled mixture of fuming

nitric acid (20 ml) and concentrated sulphuric acid (20 ml). The resulting solution was stirred at room temperature for 2 hours before ice water (50 g) was added. The precipitated solid was filtered off, washed with water and purified by precipitation from alkaline solution to give the title compound (2.5 g), m.p. 240° (decomp) (Found: C, 35.6; H, 2.5; N, 15.0. $C_8H_5N_3O_5S$ H_2O requires C, 35.2; H, 2.6; N, 15.4%).

Methyl 4-dimethylamino-5-nitrothieno[2,3-d]-pyrimidine-6-carboxylate.- Methyl 4-dimethylaminothieno-[2,3-d]pyrimidine-6-carboxylate (0.3 g) was gradually added to a stirred and cooled mixture of concentrated nitric acid (10 ml) and concentrated sulphuric acid (10 ml). The resulting solution was stirred at room temperature for 3 hours before ice water (20 g) was added. The precipitated solid was filtered off and crystallised from aqueous ethanol to give the title compound (0. 1 g), m.p. 158° (Found: C, 40.0; H, 4.0; N, 18.7. $C_{10}H_{10}N_4O_4S$ H_2O requires C, 40.0; H, 4.3; N, 18.7%).

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